The New England
Journal of Medicine

Copyright, 1954, by the Massachusetts Medical Society

Volume 250 MARCH 4, 1954 Number 9

METABOLIC ADJUSTMENTS TO NORMAL AND DISTURBED CIRCULATION IN MAN*

ELLIOT V. NEWMAN, M.D.†

NASHVILLE, TENNESSEE

IN the performance of usual physical activity, the normal circulatory apparatus is called upon to supply varying amounts of blood to tissues. It has been well demonstrated that the normal circulation does not respond with enough rapidity or quantity of blood to maintain the metabolic condition of the tissues in a compensated or "steady" state. The normal man who rises from his bed to walk makes metabolic as well as circulatory adjustments in response to the activity. Until the output of the heart and the delivery of blood to the working tissues catch up with the demands, the tissues themselves must supply energy from their stores. The circulation cannot be turned on and off instantaneously. Thus, at the beginning of an increase in activity, stores of tissue energy are used; debts are incurred. If the energy requirement is great or if the circulation is less adequate in its response, debts are continuously accumulated. An accumulation of metabolic products such as lactic acid results. The oxygen content of venous blood declines; circulation to the kidney, among other organs, falls. The subject becomes dyspneic and can no longer continue the activity.

These metabolic adjustments are part of the functional equipment of all normal people. They are made in response to the energy demands of any physical activity. One might justifiably conclude that the response of the circulatory apparatus is normally relatively incompetent and that these metabolic adjustments are made because of the relative inadequacy in the rate and quantity of circulating blood to the tissues.

In the patient with cardiac failure, the same metabolic adjustments take place. All the normal manifestations of incompetency are present in the patient with cardiac insufficiency. The difference is a matter of degree. Larger oxygen debts are accumulated more quickly and are paid back more slowly in the patient with accentuated incompetency of the circulation due to cardiac disease. Even the minimum energy requirements of basal activity may not be adequately met without these adjustments. Normal subjects are usually well equipped and accustomed to making these adjustments to circulatory inadequacy. The patient with heart disease makes relatively larger adjustments for smaller demands.

So far I have mentioned only mechanisms that seem to have no qualitative difference between the normal and the diseased subject. However, one consequence of cardiac failure is generally considered peculiar to that disease — namely, the abnormal retention of sodium chloride by the kidney. This abnormality, which is an essential part of the process of edema formation, is not usually interpreted as an abnormally accentuated pattern of metabolic adjustment occurring during the activity of people with normal circulation.

The similarity of adjustments in many respects to both the normal and the diseased circulation has encouraged a search for a stress mechanism of sodium chloride retention in the normal person that might be the basis for the accentuated phenomenon in disease. Again, it may be a quantitative, not a qualitative difference between the normal and the abnormal.

First to be examined was the excretory response pattern of patients with cardiac failure exposed to the simplest, most common stimulus in life — namely, standing and walking. An example of such a study is presented in Figure 1. This patient had just made a good recovery from moderately severe congestive heart failure with edema caused by arteriosclerotic heart disease. His exercise tolerance was still low. He could maintain no greater work output than that of walking 1 or 2 miles an hour on the level without experiencing prohibitive distress.

The test was started in the morning with the patient fasting. In the first half hour the substances used for measurement of renal circulation were injected. He initiated and maintained a water diuresis drinking 180 cc. of water every half hour throughout the test. Urine was collected at frequent intervals, and the output of sodium, chloride, potassium and phosphate measured. The amount excreted is expressed as the percentage of the amount

*The Henry Jackson Lecture of the New England Cardiovascular Society, Boston, May 11, 1953.
From the Department of Medicine, Vanderbilt University School of Medicine.

†Professor of experimental medicine and chief, Laboratories of Clinical Physiology, Vanderbilt University School of Medicine.

made available for excretion by the glomeruli of the kidney. The values are plotted on a scale that allows direct comparison of the relative changes. For example, if water and sodium excretion fell in direct proportion, the line would move the same distance

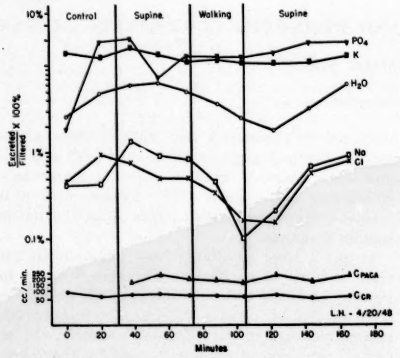


FIGURE 1. *Effect of Exercise on a Patient with Congestive Heart Failure.*

on the paper, regardless of the fact that the original value of water output was 5 per cent and that of sodium less than 1 per cent of the amount available through the glomeruli for excretion.

After the control observations in the supine position the subject walked or rather shuffled along at ½ mile an hour for thirty minutes on a motor-driven treadmill and then returned to bed. This shows the pattern of specific sodium chloride retention by the kidney with mild exercise. There is nearly a tenfold drop in sodium chloride excretion. In terms of a twenty-four-hour daily excretion, this would mean that the patient could excrete about 6 gm. of sodium chloride if supine, but only 0.6 gm. if the stimulus were continuously effective. The specificity of this mechanism for sodium chloride is demonstrated by the unchanged excretion of potassium and phosphate. A retention of water also occurs and raises the question whether there is a causal relation between water and sodium chloride retention.

It is interesting that this amount of exercise did not greatly change the renal hemodynamics, just as in the normal subject mild exercise causes little or no change in these measurements of renal function. After rest the values for water and sodium chloride excretion slowly return to control levels. Another example of this adjustment to activity is provided by a thirty-five-year-old woman with more severe congestive heart failure due to rheumatic valvular disease (Fig. 2). She was comfortable at rest but uncomfortably dyspneic with the demands of moving her body in any direction. She was allowed to walk up and down the hospital corridor at her own pace. She was able to shuffle from the door of her room to one end of the ward corridor and back in twenty minutes.

This patient demonstrated a 50 per cent drop in the measurements of renal circulation similar to that observed in a normal person undertaking severe exercise. In addition, there was a striking decrease in sodium and chloride excretion and a mild decrease in the percentage excretion of available water and potassium. At the peak of this retention, the urine contained not much more sodium chloride than ordinary tap water. A patient who could excrete continuously no more than this amount of sodium

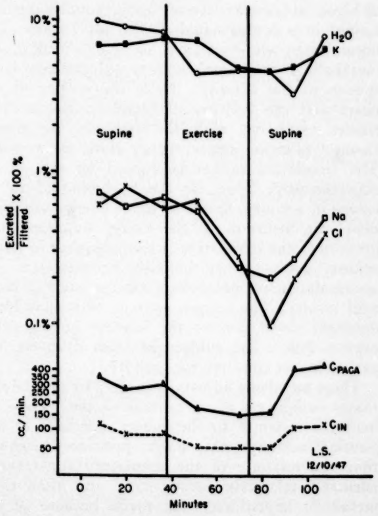


FIGURE 2. *Adjustment to Physical Activity in a Patient with Severe Congestive Heart Failure.*

chloride would require the most rigid dietary restriction to prevent abnormal accumulation — that is, an intake of less than 0.5 gm. a day. This patient had entered the hospital two weeks previously with marked edema.

With this pattern of metabolic adjustment to activity in the patient with abnormal circulation due to heart disease as a background, one can turn to a comparison with the normal subject. Does the normal person have a similar adjustment to exercise in the upright position? (In the experimental

plan for normal subjects the same standard stimulus of activity — namely, standing or walking — was used.)

The adjustments of water and electrolyte excretion to the activity of quiet standing are shown in Figure 3 in the same manner for the normal subject. After a diuresis had been established the subject stood up. This was active standing, not the passive tilt, which causes a fall in blood pressure. Pulse and blood pressure were both measured at fifteen-minute intervals. The subject was allowed

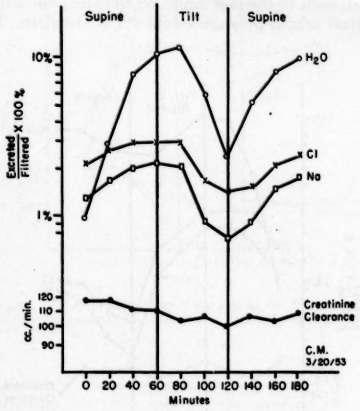


FIGURE 3. *Effect of Exercise on a Normal Subject.*

to keep comfortable by moving spontaneously but was not allowed to walk.

This activity resulted in a significant sodium chloride and water retention. This pattern is qualitatively similar to the result of standing or walking in the patient with cardiac failure. The retention was abolished promptly when the supine position was resumed. In the normal subject water excretion fell proportionately more than sodium or chloride excretion. In the patients with cardiac failure the fall of sodium and chloride was more striking than that of water excretion.

Thus, there is a pattern of sodium and chloride retention that appears to be an adjustment to standing or walking in normal people. It is possible that this same mechanism is involved in the cardiac patient.

Since in all the responses so far considered there was both sodium chloride and water retention, the question arises, Is this a specific retention of sodium and chloride? Some evidence of specificity is afforded by the observation that potassium and phosphate excretion are not altered in a parallel fashion. This is true of the normal as well as of the abnormal subject. But the question remains whether the mechanisms for sodium chloride and water retention have the same origin or are causally related.

One cause of this retention might be stimulation of secretion of the antidiuretic hormone of the posterior pituitary gland. This might cause an antidiuresis and secondarily a retention of sodium and chloride. To test this hypothesis a series of observations on the effect of injection of Pitressin were made. Figure 4 demonstrates the pattern obtained by 17 injections in 8 normal and 4 cardiac subjects. The antidiuresis was not accompanied by sodium and chloride retention in either normal or abnormal subjects. This type of experiment used a dose of Pitressin producing a water retention of comparable magnitude and duration to that obtained by the standing or exercise stimulus.

It was desired to obtain further assurance that there was no difference between the effect of injected

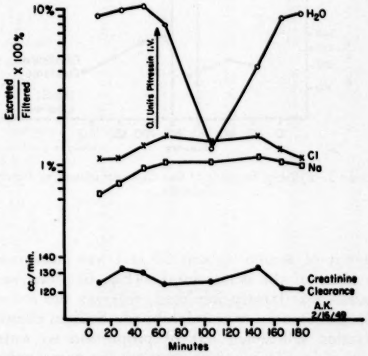


FIGURE 4. *Effect of Pitressin Injection on Normal and Cardiac Subjects.*

Pitressin and that of the antidiuretic hormone secreted by the subject's own pituitary gland. To stimulate the secretion of antidiuretic hormone, nicotine in the form of cigarette smoking was used. A subject who had not smoked for several days took one cigarette in place of the injection of Pitressin. Just as with injected Pitressin, a marked water retention resulted, with no change in sodium excretion (Fig. 5). This is further evidence that water retention is separate and not the cause or the result of sodium retention under these conditions.

A further separation of the adjustments of water and sodium chloride excretion may be accomplished

by the attempt to inhibit the secretion of the posterior pituitary gland during the exercise. Alcohol is said to cause a water diuresis by inhibiting the secretion of the antidiuretic hormone. Accordingly, the same normal subjects were given alcohol just before and during the standing period. A small amount of alcohol (about 30 cc.) was substituted for some of the water intake (Fig. 6). The antidiuresis was largely inhibited, whereas the sodium chloride retention was uninhibited. Sodium chloride excretion fell much out of proportion to water, whereas in the previous test on the same person (Fig. 3), the antidiuresis had been more striking than the sodium chloride retention.

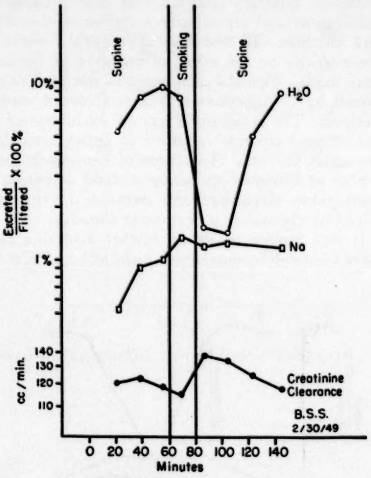


FIGURE 5. *Effect of Smoking of One Cigarette instead of Pitressin Injection.*

Up to this point in the parallel analysis of the metabolic adjustments to the normal and disturbed circulation, no adjustments have been discerned in the patient with cardiac failure that are not present qualitatively in the same form in normal man subjected to a common stress. The observations on the mechanisms of accumulating and paying off energy debts are similar in cardiac and normal subjects. These adjustments are seen readily in their acute and chronic forms in cardiac subjects. In one respect, however, the observations on the adjustments in sodium chloride and water excretion, although qualitatively similar, do not carry over very well from the normal to the cardiac subject. One does not ordinarily find an abnormal degree of accumulation of sodium chloride and water in people with normal circulation exposed to repeated or prolonged stress.

It has become a standard jest among workers in this field to comment at some point in their argument that heart failure, after all, has something to do with the heart.

One hemodynamic consequence of a failing heart is strikingly different from the normal: the elevated peripheral venous pressure, which is a reflection of the elevated diastolic filling pressure of the failing right ventricle. Thus, if a normal subject exercised all day, the peripheral venous pressure in parts such as the legs might be elevated, but a high central venous pressure would not accumulate. The normal ventricle can accomplish a large increase in output with little rise in ventricular filling pressure.

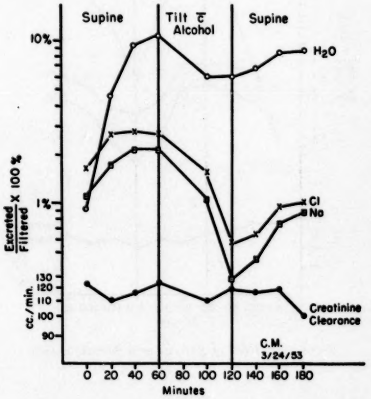


FIGURE 6. *Effect of Alcohol Administration on the Normal Subject of the Experiment Demonstrated in Figure 3.*

It has been speculated whether the normal response of sodium chloride retention to the simple tests of standing or walking could be related to increased pressure, possibly in the vessels of the legs. Accordingly, an attempt to modify the sodium chloride retention in the normal subjects was made by application of elastic bandages to the legs.

The experiment shown in Figure 7 was performed by the same subject of the study of the effect of tilting and tilting with alcohol (Fig. 3 and Fig. 6). Just before the subject stood up, his legs were wrapped with elastic bandages from the tips of the toes to the hips. This procedure did not abolish the antidiuresis, but it prevented most of the sodium and chloride retention. Never, in a normal person with this stimulus, has the sodium and the chloride

excretion remained as constant. This result is more like the response to antidiuretic hormone with simple water retention.

Evidence that these experiments are reproducible and significant is provided in Table 1. It is apparent from the creatinine clearances that in response to

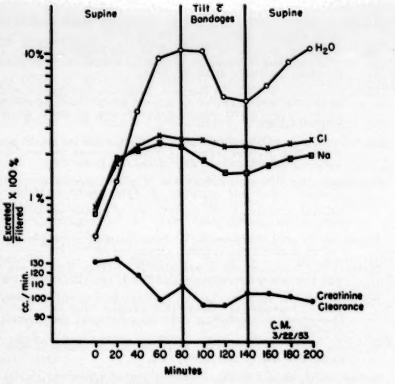


FIGURE 7. *Effect of Bandaging of the Legs of the Normal Subject of the Experiments Demonstrated in Figure 3 and Figure 6.*

tilting alone, to alcohol, or to leg wrapping, the glomerular filtration rate on the average did not fall below 90 per cent of the supine control levels. Water excretion fell to 38 per cent of its control value with tilting, and to 50 per cent on tilting with the legs wrapped. However, when alcohol was administered water excretion remained nearly constant at 93 per cent of its control value. Tilting with alcohol caused a greater drop in electrolyte excretion than tilting alone.

The most striking changes in electrolyte excretion were those of sodium. However, leg wrapping did not abolish sodium retention as effectively as alcohol abolished water retention. On the whole potassium excretion followed the same directional change as sodium and chloride. Occasionally, one finds a striking dissociation of the behavior of sodium and potassium excretion (Fig. 1 and 2).

Although there is considerable individual variation in the quantity of response to these stimuli, the direction of change is always the same. Also, there is little overlapping of the quantities in each group in spite of wide individual variation.

Much speculation can be made concerning the mechanism of this adjustment and its modification by wrapping of the legs. For the purpose of my thesis, it is sufficient to note that an alteration of the pressure relations in the legs may have a considerable modifying effect on the specific sodium chloride retention by the kidney. It seems possible that the altered venous pressure, which rises abnormally with exercise in cardiac subjects and may remain elevated at rest, causes this retention to be accentuated to the point of gross accumulation of edema. Of course, it is also possible that wrapping of the legs is effective because it prevents shifts or redistribution of blood. How this mechanism is mediated is a mystery.

Many investigators have been dissatisfied with the poor clinical correlation of the level of the peripheral venous pressure with the amount of salt retention and edema. This poor correlation cannot

TABLE 1. *Comparison of Maximum Tilt Effect with Control Period before Tilt.**

SUBJECT	CREATININE EXCRETION	WATER EXCRETION	SODIUM EXCRETION	CHLORIDE EXCRETION	POTASSIUM EXCRETION
Tilt experiments:					
M. L. P.	103	23	34	33	26
M. B.	85	21	42	51	73
M. B.	91	35	51	56	37
C. M.	90	23	34	48	54
E. V. N.	85	43	26	60	60
D. McC.	91	66	56	56	73
M. Y.	88	57	57	72	76
Averages	90	38	43	54	57
Tilt with alcohol:					
M. L. P.	77	118	31	36	42
M. B.	90	108	37	53	55
C. M.	95	57	16	21	30
D. McC.	100	112	53	38	35
M. Y.	96	69	30	39	42
Averages	92	93	33	38	41
Tilt with leg wrapping:					
M. L. P.	86	71	92	79	95
M. L. P.	98	35	65	59	48
M. B.	100	18	86	96	77
C. M.	90	55	91	86	76
C. M.	96	44	67	90	93
E. V. N.	94	29	41	52	59
E. V. N.	89	34	62	87	87
D. McC.	89	72	68	127	116
M. Y.	85	93	59	80	96
Averages	92	50	70	83	83

*Each number represents for each substance the ratio: $\frac{\text{clearance in tilt period}}{\text{clearance in control period}} \times 100$.

be explained readily, but, of course, many other factors are involved in edema formation, such as the quantity of sodium chloride intake, the elasticity of the tissues and the level of serum proteins. Perhaps there is also a marked individual variation in the sensitivity of the kidney, the organ ultimately responsible for the retention.

Possibly, it is not the resting base-line level of venous pressure that governs this reaction as much as the degree of rise in venous pressure for any given exercise. Some investigators have pointed out that the amount of edema of cardiac origin seems to correlate better with the lowered level of renal blood flow. However, it may be that the lowered renal blood flow is merely an index of the severity of the failure and these patients have a more intense exercise rise in venous pressure above an initially variable base line. Low renal blood

flow does not necessarily lead to edema. Diminished renal blood flow is common in other conditions — notably in the normal person during moderate or severe exercise, and in almost all patients with moderate and severe hypertension.

In clinical practice these adjustments to the disturbed circulation can be modified in several ways: by drugs that increase the competency of the heart muscle and thereby lower the venous pressure and raise the threshold of the salt-retention response to exercise; by reduction in the intake or intestinal absorption of sodium chloride so that there will be none to retain; by restriction of the patient's activity, which avoids accentuation of the mechanism; and by inhibition or modification of the avidity of the renal tubules for sodium chloride with drugs, allowing the available sodium chloride to be excreted.

Conclusions

The normal person and the patient with cardiac failure have qualitatively the same mechanisms of metabolic adjustment to the circulation. The patient with cardiac insufficiency differs only in duration and severity of the metabolic adjustments. The kidney is ultimately responsible for a specific retention of sodium and chloride. Specificity is demonstrated by the separation of the effects of exercise on water and sodium chloride excretion by the use of Pitressin, alcohol and bandages on the legs. The hemodynamic event that is strikingly different in cardiac failure is the rise in venous pressure. Some of the stimulus that ultimately reaches the kidney may arise in the veins, perhaps in the vessels of the legs. At any rate, alteration of the pressure relations in the legs has a considerable modifying effect on the sodium chloride retention that occurs with the common stress of standing.

Selective Bibliography

Brun, C., Knudsen, E. O. E., and Raaschou, F. Influence of posture on kidney function: fall of diuresis in erect posture. *Acta med. Scandinav.* **122**:315-331, 1945.

Dill, D. B., Edwards, H. T., Newman, E. V., and Margaria, R. Analysis of recovery from anaerobic work. *Arbeitsphysiol.* **9**:299-307, 1936.

Eggleton, M. G., and Smith, I. G. Effect of ethyl alcohol and some other diuretics on chloride excretion in man. *J. Physiol.* **104**:435-442, 1946.

Judson, W. E., Hatcher, J. D., Halperin, M. H., and Wilkins, R. W. Further studies on antidiuresis and decrease in sodium excretion during venous congestion of limbs: its prevention in normal subjects by large transfusion; its absence or presence in cardiac patients with or without congestive failure. *J. Clin. Investigation* **31**:642, 1952.

Kattus, A. A., Sinclair-Smith, B., Genest, J., and Newman, E. V. Effect of exercise on renal mechanism of electrolyte excretion in normal subjects. *Bull. Johns Hopkins Hosp.* **84**:344-368, 1949.

Landis, E. M., and Hortenstine, J. C. Functional significance of venous blood pressure. *Physiol. Rev.* **30**:1-32, 1950.

Lewis, J. M., Jr., Buie, R. M., Sevier, S. M., and Harrison, T. R. Effect of posture and of congestion of head on sodium excretion in normal subjects. *Circulation* **2**:822-827, 1950.

Lusk, J. A., Viar, W. N., and Harrison, T. R. Further studies on effects of changes in the distribution of extracellular fluid on sodium excretion: observations following compression of legs. *Circulation* **6**:911-918, 1952.

McMichael, J., and Sharpey-Schafer, E. P. Cardiac output in man by direct Fick method: effects of posture, venous pressure change, atropine, and adrenaline. *Brit. Heart J.* **6**:33-40, 1944.

Netravisesh, V. Effects of posture and of neck compression on outputs of water, sodium and creatinine. *J. Appl. Physiol.* **5**:544-548, 1953.

Ni, T.-G., and Rehberg, P. B. On influence of posture on kidney function. *J. Physiol.* **71**:331-339, 1931.

Pearce, M. L., and Newman, E. V. Some postural adjustments of salt and water excretion. *J. Clin. Investigation* **32**:594, 1953.

Peters, J. H. Determination of creatinine and creatine in blood and urine with photoelectric colorimeter. *J. Biol. Chem.* **146**:179-186, 1942.

Rice, L., Frieden, J., Katz, L. N., Elisberg, E. I., and Rosenberg, E. Case of spontaneous thrombosis of superior vena cava with some observations on mechanism of edema formation. *Am. Heart J.* **43**: 821-828, 1952.

Sanderson, P. H. Potentiometric determination of chloride in biological fluids. *Biochem. J.* **52**:502-505, 1952.

Sinclair-Smith, B. C., et al. Effects of posterior pituitary extract and smoking on water, sodium and chloride excretion in normal subjects and in patients with congestive cardiac failure. *Bull. Johns Hopkins Hosp.* **87**:221-234, 1950.

Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S. Cardiac output in male subjects as measured by technique of right atrial catheterization: normal values with observations on effect of anxiety and tilting. *J. Clin. Investigation* **24**:326-331, 1945.

Strauss, M. B., Davis, R. K., Rosenbaum, J. D., and Rossmeisl, E. C. Production of increased renal sodium excretion by hypotonic expansion of extracellular fluid volume in recumbent subjects. *J. Clin. Investigation* **31**:80-86, 1952.

Strauss, M. B., Rosenbaum, J. D., and Nelson, W. P., III. Effect of alcohol on renal excretion of water and electrolyte. *J. Clin. Investigation* **29**:1053-1058, 1950.

Weiss, S., and Ellis, L. B. Oxygen utilization and lactic acid production in extremities during rest and exercise: in subjects with normal and in those with diseased cardiovascular systems. *Arch. Int. Med.* **55**:665-680, 1935.

Welt, L. G., and Orloff, J. Effects of increase in plasma volume on metabolism and excretion of water and electrolytes by normal subjects. *J. Clin. Investigation* **30**:751-761, 1951.

CUTANEOUS ANERGY AND HODGKIN'S DISEASE*

W. Wilson Schier, M.D.†

BROOKLYN, NEW YORK

THE association of the reticuloendothelial system with immunity is well known. It is not surprising, therefore, that disturbance of this system modifies the pattern of immunity. Blockage of the reticuloendothelial system by inert particulate matter has been shown to cause a temporary depression of antibody production.[1] The association of Hodgkin's disease with a negative tuberculin reaction is familiar.[2] Speculation concerning the significance of this phenomenon has been centered in large part on the relation of tuberculosis to Hodgkin's disease. Much attention has been given to establishing the tubercle bacillus in an etiologic role. Sternberg,[3] as early as 1898, was convinced that Hodgkin's disease represented a variety of response to the tubercle bacillus. The situation was not unlike that which has prevailed regarding the etiology of sarcoidosis. That the negative tuberculin reaction in the majority of patients with Hodgkin's disease is probably not specific requires emphasis.

Dubin[4] called attention to the poverty of the immunologic mechanism in Hodgkin's disease. He noted the anergy to tuberculin; the lower incidence of positive serologic reactions for syphilis; the inability to produce antibodies against coexistent brucellosis; and the failure of a patient with Hodgkin's disease to respond to typhoid vaccine by production of antibodies. Larson and Tomlinson[5] observed the diminished production of antibodies to pneumococcus polysaccharide Types 2 and 3 in 3 patients with Hodgkin's disease. Similarly, Friou[6] reported reduced skin reactions to several antigens (oidiomycin, trichophytin, mumps and tuberculin) in patients with sarcoidosis. The observations that follow describe cutaneous anergy to these antigens in Hodgkin's disease.

Materials and Methods

The reactions to the intracutaneous injections of five antigens and histamine were studied in 114 persons, of whom 33 were patients with Hodgkin's disease, 64 were controls and the remainder had other systemic disorders. The diagnosis of Hodgkin's disease was established by lymph-node biopsy.

The control group consisted of patients with no evidence of Hodgkin's disease; they were without fever and had normal white-cell and red-cell counts. They were hospitalized for the treatment of such conditions as duodenal ulcer, diabetes mellitus, cirrhosis of the liver and rheumatic heart disease. Some were convalescing from surgical operation. None were women. The mean age of the control group was forty and a half years, and that of the patients with Hodgkin's disease thirty-three and eight-tenths years. In the control group there were no significant differences in diameter or frequency of positive reactions between whites and Negroes, between normal persons and those with disease or between those of different ages. Cachectic and severely ill patients were excluded from the study because of the known decrease in the immune response in such persons. Only ambulatory patients with Hodgkin's disease were included. In Table 1, the severity of the disease, is classified from + to +++.

Seventeen patients with miscellaneous disorders were also studied. These consisted of chronic leukemias, lymphosarcoma, reticulum-cell sarcoma, aplastic anemia, brucellosis, splenomegaly, sarcoidosis and giant-follicle lymphoblastoma (Table 2).

Purified protein derivative (P.P.D.) of intermediate strength (0.0002 mg.) was employed to determine the reaction of each subject to tuberculin. Simultaneously, tests were made with histamine phosphate (0.05 cc.), 1:1000 dilution, and four other unrelated antigens that, like tuberculin, induce delayed responses. These were mumps virus, *Candida albicans*, *Trichophyton gypseum* and normal allantoic fluid of chick embryo, as a control for the mumps virus antigen, which is cultured on chick-embryo allantoic fluid. Extracts of *C. albicans* and *T. gypseum* were used in a dilution of 1:150. The antigens were injected in 0.1-cc. doses intracutaneously, and the reactions read after forty-eight hours. The greatest diameter of the area of edema (3 mm. or larger) was measured. Erythema was not measured because of the difficulty of accurate estimation in pigmented persons. Separate syringes for each antigen were employed to avoid mixed reactions.

Analysis of Data

Comparisons of quantitative variates between the experimental and control cases (Table 3) were made by two methods: student's "t", which assumes a Poisson distribution of the variable in the population, and Mann–Whitney U-test, which is distribution free — that is, it makes no assumption about the form of distribution.

In no case did the two tests lead to different conclusions of statistical significance. The P values given below, which indicate the risk of falsely concluding that a true difference exists, were those

*From the Medical Services, Veterans Administration hospitals, Bronx and Brooklyn.

†Clinical instructor in medicine, Yale University School of Medicine; assistant chief of professional services, Veterans Administration Hospital.

yielded by the U test, the more conservative of the two tests.

Histamine

The means were virtually identical: control, 17.2 mm., and patients with Hodgkin's disease, 17.3 mm. Comparisons of these two groups revealed no statistically significant variation to the intracutaneous injection of histamine (Fig. 1). The reaction was an immediate one measured twenty minutes after injection.

Mumps Control

Normal allantoic fluid of chick embryo elicited 1 positive reactor in 114 tests. This was in subject 60 of the control group.

Mumps Antigen

The control group had 55 (86 per cent) positive reactors as compared with 6 (18 per cent) of the patients with Hodgkin's disease, in 5 of whom the reaction was smaller than that in any of the controls. Clinically, a reaction larger than 10 mm. was considered to indicate relative immunity. The group difference in average diameter was highly significant (p less than 0.001).

Candida albicans

Positive reactors were found in 59 of the control group (92 per cent). The patients with Hodgkin's disease included 7 reactors (21 per cent). Here, too, the group difference in average size of reactions was highly significant (p less than 0.001).

TABLE 1. *Data in Patients with Hodgkin's Disease.*

Case No.	Age	Diagnosis	Allergy	History of Mumps	Duration of Disease	Clinical Estimate of Severity	Cutaneous Reaction to Histamine
	yr.						mm.
1	36	Hodgkin's sarcoma	0	?	4 wk.	+	15
2	42	Hodgkin's sarcoma	0	+	9 mo.	+	17
3	36	Hodgkin's sarcoma	0	?	2 mo.	++	15
4*	34	Hodgkin's paragranuloma	Seasonal allergic rhinitis	?	1 yr.	+	22
5	31	Hodgkin's granuloma	0	+	3 yr.	++	17
6	59	Hodgkin's granuloma	0	?	4 yr.	+	13
7	22	Hodgkin's granuloma	0	+	4 mo.	++	21
8	25	Hodgkin's granuloma	Sensitivity to horse serum & penicillin	+	6 mo.	+	20
9	26	Hodgkin's granuloma	0	+	2 yr.	+	24
10	29	Hodgkin's granuloma	Sensitivity to aspirin	+	5 yr.	++	14
11	35	Hodgkin's granuloma	0	?	2 yr.	++	20
12	30	Hodgkin's granuloma	0	0	8 yr.	+++	18
13	28	Hodgkin's sarcoma	0	?	6 yr.	++	12
14	30	Hodgkin's granuloma	0	?	3 yr.	+	13
15	36	Hodgkin's granuloma	0	+	2 yr.	++	19
16	34	Hodgkin's granuloma	0	+	3 yr.	+++	17
17	30	Hodgkin's granuloma	0	0	8 yr.	++	17
18	43	Hodgkin's granuloma	0	+	4 mo.	++	13
19	24	Hodgkin's granuloma	0	+	2 yr.	++	17
20	32	Hodgkin's paragranuloma	0	+	2 yr.	+	18
21	36	Hodgkin's sarcoma	0	0	7 yr.	+++	16
22	33	Hodgkin's granuloma	Sensitivity to penicillin	?	18 mo.	++	15
23	33	Hodgkin's granuloma	0	0	12 mo.	+++	15
24	26	Hodgkin's granuloma	0	+	12 mo.	+	20
25	26	Hodgkin's granuloma	0	?	12 mo.	++	18
26	60	Hodgkin's granuloma	0	+	19 mo.	+++	20
27	31	Hodgkin's granuloma	0	+	3½ yr.	++	15
28	27	Hodgkin's granuloma	0	?	3 yr.	+++	15
29	47	Hodgkin's granuloma	0	?	4 yr.	++	19
30	25	Hodgkin's granuloma	0	0	18 mo.	+	19
31	40	Hodgkin's granuloma	Sensitivity to penicillin †	+	9 mo.	+	18
32	31	Hodgkin's granuloma	0	0	3 mo.	+	16
33	37	Hodgkin's granuloma	0	+	15 mo.	+	24

*Amelioration of allergic rhinitis 1 yr. before diagnosis of Hodgkin's disease.
†Current therapy.

Trichophyton gypseum

There were positive reactors in 45 (72 per cent) of the control group and 9 (27 per cent) of the patients with Hodgkin's disease. The patients with Hodgkin's disease gave a significantly smaller response (p less than 0.001).

Discussion

Six of the patients with Hodgkin's disease had received cortisone, and 15 nitrogen mustard; 24 had been treated by irradiation. All these modalities may affect the immune pattern of the subject. Before the cutaneous anergy is attributed to the disease, the possible effects of the therapy received must be weighed. Five patients (Cases 1, 2, 3, 4 and 32 in Table 1) received none of these modalities.

Table 1 (*Concluded*).

Case No.	Cutaneous Reaction to Mumps Control Fluid	Cutaneous Reaction to Mumps Antigen	Cutaneous Reaction to *Candida albicans*	Cutaneous Reaction to *Trichophyton gypseum*	Cutaneous Reaction to Tuberculin	Interval Since Last Radiation Dosage	Nitrogen Mustard Therapy	ACTH or Cortisone Therapy
	mm.	mm.	mm.	mm.	mm.			
1	0	0	0	0	15	0	0	0
2	0	0	3	3	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	3	13	0	0	0	0
5	0	0	0	3	4	6 wk.	0	0
6	0	8	10	5	9	4 wk.	1 course (2 yr.)	0
7	0	12	0	0	0	0	1 course (3 mo.)	0
8	0	13	12	15	15	3 mo.	0	0
9	0	8	6	0	0	2 yr.	0	0
10	0	0	0	0	0	4 mo.	1 course (12 mo.)	0
11	0	0	0	0	0	3 mo.	1 course (10 mo.)	0
12	0	0	0	0	0	0†	1 course (13 mo.)	0
13	0	0	0	0	0	4 mo.	0	0
14	0	0	0	0	0	2 wk.	0	Cortisone (100 mg. daily for 1 wk.)
15	0	0	0	10	0	0	0	0
16	0	0	0	10	0	2 wk.		
17	0	0	0	0	0	2 mo.	0	0
18	0	0	0	0	0	4 mo.	0	0
19	0	0	0	0	0	4 mo.	2 courses (12 mo.)	Cortisone (100 mg. daily for 1 wk.)
20	0	8	0	0	10	0	0	0
21	0	0	0	0	0	0†	3 courses (34 mo.)	
22	0	0	9	0	0	12 mo.	0	
23	0	0	0	0	0	10 days	2 courses (3 mo.)	ACTH (1 yr. previously)
24	0	0	0	0	0	6 mo.	2 courses (2 mo.)	0
25	0	0	0	0	0	0	1 course (2 mo.)	0
26	0	0	0	0	0	10 days	1 course (3 mo.)	0
27	0	0	0	0	8	4 mo.	†	0
28	0	0	0	0	5	†	2 courses (2 mo.)	0
29	0	0	0	3	0	2 yr.	0	ACTH (75 mg. daily for 60 days) Cortisone (March, 1953)
30	0	0	10	0	0	†	2 courses (4 mo.)	
31	0	0	0	0	0	6 mo.	1 course (6 wk.)	Cortisone (4 mo. previously)
32	0	0	0	0	4	0	0	0
33	0	12	0	0	0	13 mo.	0	0

Tuberculin

Similarly, 46 (72 per cent) of the control group gave positive skin reactions to P.P.D. of intermediate strength. Seven (21 per cent) of the patients with Hodgkin's disease gave reactions (p less than 0.001). This accords with the observations of Steiner[2] and others.[7]

Dougherty, Chase and White[8] called attention to the relation between adrenal hormones and antibody formation and presented evidence that the administration of ACTH to immunized rabbits resulted in a liberation of antibodies from lymphoid tissue. Subsequent investigation revealed no sig-

nificant rise in antibody titer under these conditions.[9, 10] In addition numerous studies in man failed to demonstrate an effect of cortisone on circulating antibody titers[11] or on the production of antibodies in response to specific sensitization.[12] More recent experimental studies in animals, however, employing careful quantitative immunologic technics, have indicated that these hormones significantly inhibit the rise in antibody titers that follows specific sensitization.[13, 14]

It is generally considered that cortisone is incapable of inhibiting the union of antigen and antibody. This view is based on the failure of most workers to prevent anaphylaxis in most species. An important factor in determining response is not only the species of animal but also the time and dosage of antigen and hormones. An inhibition of the tuberculin reaction by comparatively large doses of hormones has been reported by Long and Favour.[15] It appears that the effects of the hormones in this phenomenon depend on the interference with some aspect of tissue reactivity. Fischel[16] emphasizes the point that although it has been clearly demonstrated that antibody synthesis is depressed by cortisone, the depression is small in extent and occurs only when extraordinarily large quantities of the hormones are used. Loveless[17] has shown unchanged skin reactivity to ragweed antigen in sensitive patients who received cortisone although they were clinically relieved of symptoms. The 6 patients in this study were given 100 mg. a day or less. Their cutaneous responses to the antigens were not qualitatively or quantitatively different from those who were not receiving cortisone. It is Fischel's opinion that moderate doses of cortisone do not appreciably inhibit the tuberculin reaction.

The response of these patients to histamine was similar to that in the control group — the average size of the wheal produced in each group was 17 mm. The altered reactivity of the tissue in the patients with Hodgkin's disease is therefore not a result of inability to react to histamine.

Fifteen of the 33 patients had received nitrogen mustard. One of 4 who had had this therapy within two months of this study showed regression of lymph nodes. The others had no change in the size of the lymph nodes. Three, however, exhibited complete skin anergy. The remaining 11 patients had received the nitrogen mustard therapy nine months to two years before skin testing. There is some evidence of a temporary suppression of antibody formation with large doses of nitrogen mustard given simultaneously with the antigen in laboratory animals.[18] Hektoen and Corper,[19] in 1921, used mustard gas to inhibit antibody formation in the rabbit. After Gilman and Philips[20] had described the clinical effects of the nitrogen mustards in 1946 these agents also were found to depress antibody production in the goat.[21, 22] Jimenez Diaz et al.[23] reported suppression in man. In this study, however, it is fair to assume that the occasion for antibody formation occurred before the administration of nitrogen mustard.

In a review of the effects of x-rays on immunity, Taliaferro[24] made the following statement:

> Small amounts of X-rays, often administered locally, sometimes enhance antibody formation and the immunity of experimental laboratory animals to non-living antigens and certain infections. This conclusion has also been reached with respect to a wide range of infections in man but may

TABLE 2. *Data in Patients with Miscellaneous Diseases.*

Case No.	Age	Diagnosis	Allergy	History of Mumps	Duration of Disease	Cutaneous Reaction to Histamine
	yr.					mm.
1	56	Brucellosis	0	0	6 mo.	18
2	58	Splenomegaly (cause?)	0	?	10 yr.	15
3	45	Chronic myelogenous leukemia	0	0	6 mo.	17
4*	28	Chronic myelogenous leukemia	Seasonal rhinitis	0	2 yr.	18
5	58	Chronic myelogenous leukemia	0	+	2 yr.	10
6	24	Chronic myelogenous leukemia	Sensitivity to codeine & dromeran	+	3 yr.	18
7	46	Chronic lymphatic leukemia	0	0	1 yr.	16
8	74	Reticulum-cell sarcoma	0	?	4 mo.	16
9	26	Lymphosarcoma	0	+	1 yr.	20
10	56	Multiple myeloma	0	+	6 mo.	15
11	30	Lymphogranuloma venereum	0	+	4 mo.	15
12	62	Chronic lymphatic leukemia and lymphosarcoma	0	+	2 yr.	30
13	30	Sarcoidosis	0	?	8 mo.	18
14	35	Lymphosarcoma	0	+	2 mo.	24
15	33	Giant-follicle lymphoblastoma	0	?	18 mo.	20
16	62	Chronic lymphatic leukemia	0	?	18 mo.	24
17†	26	Aplastic anemia	0	+	3½ yr.	21

*Disappearance of hay fever 1 yr. before diagnosis of leukemia.
†150 transfusions in 3½ yr.
‡Current, with skin tests.

not in all cases be justified because of inadequate controls. The mechanism involved in an enhanced immunity by X-rays has been variously explained but has not been adequately clarified . . . .

X-rays approaching lethal amounts when administered to the entire body often decrease host immunity to specific infections and lower antibody formation . . . .

This interesting paper extensively reviews the literature to 1950. Dixon et al.[25] indicate that total body irradiation in rabbits is required twelve hours or more before injection of the antigen to inhibit antibody generation.

These conditions did not prevail in the patients with Hodgkin's disease observed. As with nitrogen mustard irradiation must be given shortly before the antigen is injected to block antibody formation. The dosage must permit survival of the animal and must be total body irradiation. Sparing even small parts of the body greatly enhances resistance to irradiation. Jacobson and his associates[26] demonstrated that shielding the spleen during total body irradiation permitted animals to survive otherwise fatal radiation and produce antibodies.

None of the patients described received other than local irradiation. Therefore, because of the timing of the exposure to antigen and radiation and also because the radiation was not total body radiation, the effects on the skin reactions were relatively less significant.

The cumulative effects of these modalities of therapy might have influenced the appearance of the anergy, but only 1 patient had received all three agents: nitrogen mustard, x-rays and ACTH or cortisone. There was no association between the skin reactions to the antigens and the amount of therapy received. Likewise, there was no positive correlation between the degree or duration of the illness and reactivity of the skin.

Several other forms of lymphoma were investigated in addition to Hodgkin's disease. Four patients with chronic myelogenous leukemia demonstrated some decreased reactivity to the antigens. It was not total as in many of the cases of Hodgkin's disease, the degree of response being between that of the normal subjects and the patients with Hodgkin's disease. (The small number of cases precludes meaningful statistical analysis.)

One patient with reticulum-cell sarcoma was completely unreactive to the antigens. This is interesting in view of the current opinion that Hodgkin's disease probably arises from the reticulum cells.[27] Whether this primordial cell is considered lymphoblast, myeloblast or plasmablast is less important than the observation that the earliest change in Hodgkin's disease is the proliferation of the reticulum cells.[28]

In 2 patients with chronic lymphatic leukemia the skin reactions were much like those in the 4 with chronic myelogenous leukemia, being intermediate between effect observed in the normal subjects and that in the patients with Hodgkin's disease. One patient with lymphosarcoma and lymphatic leukemia, 1 with splenomegaly of undetermined etiology, 1 with brucellosis and 1 with aplastic anemia reacted similarly. It is not possible to separate from this group of patients the relatively reactive patients with Hodgkin's disease, 6 of whom showed more than one positive skin test. Only 2 had more than two positive reactions.

Eleven of the control group gave a history of clinical allergy. However, the size of the reactions

TABLE 2 (*Concluded*).

CASE NO.	CUTANEOUS REACTION TO MUMPS CONTROL FLUID	CUTANEOUS REACTION TO MUMPS ANTIGEN	CUTANEOUS REACTION TO *C. albicans*	CUTANEOUS REACTION TO *T. zypseum*	CUTANEOUS REACTION TO TUBERCULIN	INTERVAL SINCE LAST RADIATION DOSAGE	NITROGEN MUSTARD THERAPY	ACTH THERAPY
	mm.	mm.	mm.	mm.	mm.			
1	0	0	0	4	5	0	0	0
2	0	0	4	0	5	0	0	0
3	0	4	5	3	3	0	0	0
4*	0	0	0	0	0	1 mo.	0	100 mg. daily — (current) 2 mo. previously
5	0	0	0	8	0	1 mo.	0	0
6	0	8	9	3	0	4 mo.	0	0
7	0	0	15	5	0	10 mo.	0	0
8	0	0	0	0	0	0	0	0
9	0	0	8	6	0	0‡	0	0
10	0	3	10	12	0	0	0	0
11	0	8	9	10	10	0	0	0
12	0	6	0	0	0	3 wk.	1 course (3 mo.)	0
13	0	0	16	14	0	0	0	0
14	0	5	0	0	5	0‡	0	0
15	0	13	8	12	0	0	1 course (7 mo.)	0
16	0	0	10	15	0	0‡	0	0
17†	0	8	0	0	0	0	0	0

TABLE 3. *Data in Control Subjects.*

SUBJECT NO.	AGE	DIAGNOSIS	HISTORY OF ALLERGY	HISTORY OF MUMPS	DURATION OF DISEASE
	yr.				
1	29	Pilonidal sinus (operation 4 wk. previously)	0	?	3 yr.
2	38	Duodenal ulcer with hemorrhage (6 wk. previously)	Asthma (4-16 feathers)	?	6 yr.
3	47	Hypertensive cardiovascular disease	0	?	9 yr.
4	37	Duodenal ulcer,	0	0	10 yr.
5	26	Cardiomegaly (cause?)	0	?	1 yr.
6	54	Duodenal ulcer	0	+	30 yr.
7	27	Pilonidal sinus (operation 1 mo. previously)	0	+	1 yr.
8	40	Diabetes mellitus	0	+	9 yr.
9	57	Cirrhosis of liver	0	0	8 yr.
10	56	Duodenal ulcer with obstruction	0	+	20 yr.
11	48	Duodenal ulcer	0	0	10 yr.
12	28	Duodenal ulcer	0	+	5 yr.
13	60	Rheumatic heart disease with mitral stenosis	0	+	2 yr.
14	38	Duodenal ulcer	0	0	5 yr.
15	59	Duodenal ulcer with hemorrhage	Seasonal hay fever	+	10 yr.
16	28	Hernia (before operative repair)	0	+	3 yr.
17	50	Alcoholism	Asthma (10 yr.)	+	20 yr.
18	32	Diabetes mellitus	0	?	5 yr.
19	36	Facial paralysis	0	?	3 mo.
20	28	Appendicitis (1 wk. after appendectomy)	0	+	1 wk.
21	32	Duodenal ulcer	Asthma (in childhood)	?	10 yr.
22	59	Healed thrombophlebitis	0	+	3 mo.
23	28	Duodenal ulcer	0	?	5 yr.
24	46	Duodenal ulcer	0	+	9 yr.
25	46	Duodenal ulcer	0	0	5 yr.
26	37	Ileitis	0	?	1 yr.
27	29	Viral pericarditis	0	+	3 mo.
28	28	Infectious mononucleosis	0	+	2 mo.
29	28	Duodenal ulcer	Hay fever (ragweed)	+	10 yr.
30	30	None (normal)	Hay fever (ragweed)	?	—
31	28	Infectious mononucleosis (hepatitis)	0	?	4 mo.
32	71	Duodenal ulcer	0	—	21 yr.
33	59	Rheumatic heart disease (inactive)	Sensitivity to dust, feathers and penicillin	?	34 yr.
34	62	Hypertensive cardiovascular disease, with aortic stenosis	0	0	4 yr.
35	54	Hypertensive cardiovascular disease, with angina	0	?	2 mo.
36	70	Cor pulmonale	0	?	6 mo.
37	56	Hypertensive cardiovascular disease & cerebrovascular accident	0	0	3½ yr.
38	38	Hypertensive cardiovascular disease	0	?	10 yr.
39	28	Rheumatic heart disease (inactive)	Hay fever	0	8 yr.
40	56	Hypertensive cardiovascular disease	0	0	3 yr.
41	40	Aortic stenosis, with coronary occlusion	?	?	2 yr.
42	45	Coronary occlusion	Hay fever (ragweed)	?	2 mo.
43	35	Hypertensive cardiovascular disease	0	+	3 yr.
44	26	Rheumatic heart disease	0	0	3 yr.
45	32	Coronary-artery disease	0	+	2 mo.
46	35	Varicose veins	Sensitivity to penicillin	0	5 yr.
47	67	Inguinal hernia	0	?	1 yr.
48	29	Pilonidal cyst (postoperative)	0	?	6 yr.
49	61	Hemorrhoids	0	?	9 yr.
50	27	Pilonidal sinus (operation 5 yr. previously)	0	0	10 yr.
51	41	Varicose veins	0	?	20 yr.
52	21	Plastic surgery (scalp)	0	+	(Operation 3 wk. previously)
53	57	Amputation revision	0	+	(Operation 3½ mo. previously)
54	36	Diabetes mellitus	0	?	4 yr.
55*	33	Diverticulitis, with adhesions	0	+	(2 operations 3 yr. previously)
56	38	Addison's disease	0	?	6 yr.
57	43	Cirrhosis of liver	0	?	10 yr.
58	31	Headache (post trauma)	0	?	7 yr.
59	40	Furunculosis	0	0	3 mo.
60	34	Varicose veins	Rash from tomatoes	+	4 yr.
61	33	Cirrhosis of liver	0	+	2 mo.
62	20	Rheumatoid arthritis	0	+	2 yr.
63	30	Diabetes mellitus	0	+	5 yr.
64	31	Gouty arthritis	0	+	8 yr.

*Anergy unexplained.

TABLE 3 (*Concluded*).

SUBJECT NO.	CUTANEOUS REACTION TO HISTAMINE	CUTANEOUS REACTION TO MUMPS CONTROL FLUID	CUTANEOUS REACTION TO MUMPS ANTIGEN	CUTANEOUS REACTION TO *C. albicans*	CUTANEOUS REACTION TO *T. gypseum*	CUTANEOUS REACTION TO P.P.D.	MEDICATION
	mm.	mm.	mm.	mm.	mm.	mm.	
1	15	0	4	10	8	17	0
2	14	0	12	3	8	16	Banthine & Amphojel
3	22	0	15	12	8	18	Digitalis
4	20	0	18	16	3	20	Banthine & Amphojel
5	14	0	10	10	0	18	0
6	13	0	20	10	3	15	Banthine & Amphojel
7	17	0	6	13	9	14	0
8	14	0	3	0	13	14	Insulin
9	18	0	0	13	6	12	Diuretics
10	12	0	16	13	10	12	Banthine
11	18	0	8	13	15	12	Banthine & phenobarbital
12	13	0	4	20	13	10	Banthine & phenobarbital
13	19	0	8	14	7	10	Digitalis & Mercuhydrin
14	16	0	0	17	10	10	Banthine & Gelusil
15	16	0	18	15	16	10	Banthine & diet
16	16	0	19	10	8	6	0
17	18	0	14	23	0	5	Vaponephrine, penicillin & vitamins
18	14	0	8	15	18	5	25 units of protamine zinc insulin
19	16	0	13	14	4	5	0
20	18	0	6	12	7	4	0
21	16	0	12	15	0	3	Banthine & Gelusil
22	19	0	6	15	23	0	0
23	20	0	6	15	18	0	Banthine & antacids
24	16	0	7	0	8	0	Banthine & antacids
25	18	0	12	12	8	17	Banthine & antacids
26	22	0	13	10	0	25	Banthine & phenobarbital
27	18	0	11	14	8	15	0
28	24	0	18	20	0	0	0
29	17	0	12	14	10	10	Banthine & Gelusil
30	18	0	15	12	0	4	0
31	15	0	3	10	15	0	0
32	18	0	10	8	10	5	Banthine & Gelusil
33	22	0	0	0	5	0	Digoxin
34	16	0	5	35	0	12	Digoxin
35	19	0	6	5	10	8	Digitoxin & Mercuhydrin
36	12	0	4	18	5	0	0
37	16	0	5	10	8	0	0
38	23	0	9	6	8	62	*Rauwolfia serpentina* & Veriloid
39	18	0	0	17	15	0	None
40	18	0	15	12	0	6	*Rauwolfia serpentina* & Veriloid
41	16	0	7	16	13	10	Nitroglycerin
42	20	0	7	19	0	10	0
43	26	0	6	13	0	9	Hexamethonium & Apresoline
44	19	0	0	12	19	0	Penicillin & nitroglycerin
45	21	0	0	4	8	28	0
46	19	0	5	6	0	0	0
47	17	0	0	12	0	20	0
48	16	0	15	18	0	0	0
49	16	0	0	10	0	8	0
50	15	0	12	0	12	10	0
51	17	0	12	16	0	13	0
52	17	0	3	20	8	0	0
53	17	0	16	14	6	8	0
54	14	0	10	11	8	7	75 units of NPH insulin; 1 gm. of chlortetracycline daily.
55	15	0	3	0	0	0	Sulfonamide
56	14	0	12	12	8	5	Cortisone; DOCA, 12.5 mg. twice daily.
57	17	0	17	8	10	13	Diet
58	14	0	15	18	12	10	0
59	17	0	18	18	0	0	0
60	18	8	10	6	0	11	0
61	18	0	12	15	6	5	Diet
62	18	0	6	8	0	0	0
63	13	0	12	15	8	0	45 units of NPH insulin daily
64	17	0	13	20	10	0	Aspirin & Antabuse

to the skin-testing antigens was not significantly different from that of the other controls. Five had a history of transient skin allergy.

Six of the patients with Hodgkin's disease gave histories of clinical allergies. The comparatively large number of these patients and of the controls reporting histories of allergies was probably a consequence of detailed questioning. None of the patients with Hodgkin's disease had clinical allergies associated with their current disease. One had a history of hay fever since childhood, with associated seasonal asthma; without change in environment or medication, he noticed considerable amelioration of symptoms a year before the onset of Hodgkin's disease. One patient with myelogenous leukemia gave a history of complete disappearance of hay fever a year before clinical signs of chronic myelogenous leukemia appeared. Hoster,[27] in a review of Hodgkin's disease, notes that an allergic history is seldom reported. In this regard it was interesting that 2 patients with Hodgkin's disease who had severe pruritus and skin changes not unlike chronic eczematoid dermatitis were completely unreactive to the antigens used in this study.

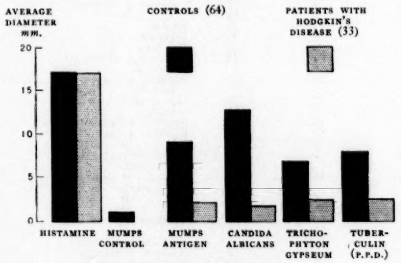


FIGURE 1. *Cutaneous Response to Antigens.*

Dubin's[4] observations on the deficiency of the immune mechanism in Hodgkin's disease and measurements of antibody response by Larson and Tomlinson[5] to pneumococcus polysaccharide in 3 patients with Hodgkin's disease have already been noted. Observations on the attenuated production of agglutinins to typhoid antigen by 6 patients with Hodgkin's disease are in agreement with their results.[29]

Hodgkin's disease offers a fruitful field for the study of the mechanism of immunity. However, it should be noted that cutaneous anergy in this condition is a nonspecific response since similar observations have been made by Friou[6] in sarcoidosis.

If there is a defect in the immune mechanism it would be expected that patients with Hodgkin's disease would be more susceptible to infections, including tuberculosis. This has been strongly indicated by analysis of the immediate causes of death in such cases.[27]

The protean symptomatology of Hodgkin's disease and the secondary effects of radiation and nitrogen mustard sometimes obscure the terminal events. However, tuberculosis is associated more frequently with Hodgkin's disease than with the leukemias.

A number of interesting problems regarding the defect in the immune mechanism in Hodgkin's disease are suggested. The failure to elicit a normal cutaneous reaction may be a result of a block at one or more places in the immune mechanism. Production of antibodies may be inhibited. Whether inhibiting substances are present in the serum of these patients is not known. Lack of effective antibodies or complement or both, may be a factor in anergy.

SUMMARY

A study of the cutaneous reactions in 33 patients with Hodgkin's disease to the antigens of mumps virus, *Candida albicans*, *Trichophyton gypseum* and purified protein derivative of tuberculin revealed a striking cutaneous anergy. The reaction to histamine was normal, however.

One patient with Hodgkin's disease and another with myelogenous leukemia had marked amelioration of allergic rhinitis and asthma a year before the diagnosis of the principal diseases had been made.

The site of the block in the immune mechanism has not been delineated. It is suggested that patients with Hodgkin's disease fail to produce demonstrable antibodies in normal quantities.

The attenuated cutaneous reactions in several other diseases — chronic myelogenous leukemia, chronic lymphatic leukemia, lymphosarcoma and reticulum-cell sarcoma — are described.

I am indebted to Drs. Lyle Fulkerson and Arthur Roth for assistance. The statistical analyses were accomplished by Dr. Jacob Cohen, of the Department of Clinical Psychology, Bronx Veterans Administration Hospital. The skin-test antigens for mumps were supplied by the Lederle Laboratories Division, American Cyanamide Company, Pearl River, New York, through the courtesy of Dr. Victor Cabasso, Section of Viral and Rickettsial Research.

REFERENCES

1. Jaffe, R. H. Reticulo-endothelial system in immunity. *Physiol. Rev.* 11:277-327, 1931.
2. Steiner, P. E. Etiology of Hodgkin's disease: skin reactions to avian and human tuberculin proteins in Hodgkin's disease. *Arch. Int. Med.* 54:11-17, 1934.
3. Sternberg, C. Über eine eigenartige unter dem Bilde der Pseudoleukämie verlaufende Tuberculose des lymphatischen Apparates. *Ztschr. f. Heilk.* 19:21-90, 1898.
4. Dubin, I. N. Poverty of immunological mechanism in patients with Hodgkin's disease. *Ann. Int. Med.* 27:898-913, 1947.
5. Larson, D. L. and Tomlinson, L. J. Quantitative antibody studies in man. III. Antibody response in leukemia and other malignant lymphomata. *J. Clin. Investigation* 32:317-321, 1953.
6. Friou, G. Study of cutaneous reactions to oidiomycin, trichophytin, and mumps skin test antigens in patients with sarcoidosis. *Yale J. Biol. & Med.* 24:533-539, 1952.
7. Parker, F., Jr., Jackson, H., Jr., Fitzhugh, G., and Spies, T. D. Studies of diseases of lymphoid and myeloid tissues. IV. Skin reactions to human and avian tuberculin. *J. Immunol.* 22:277-282, 1932.

8. Dougherty, T. F., Chase, J. H., and White, A. Pituitary-adrenal cortical control of antibody release from lymphocytes: explanation of anamnestic response. *Proc. Soc. Exper. Biol. & Med.* **58**: 135-140, 1945.

9. Eisen, H. N., Mayer, M. M., Moore, D. H., Tarr, R. R., and Stoerk, H. C. Failure of adrenal cortical activity to influence circulating antibodies and gamma globulin. *Proc. Soc. Exper. Biol. & Med.* **65**:301-306, 1947.

10. de Vries, J. A. Effect of adrenocorticotrophic hormone on circulating antibody levels. *J. Immunol.* **65**:1-5, 1950.

11. Massell, B. F., et al. Effect of ACTH on antistreptolysin O and gamma globulin response to hemolytic streptococcal infection (scarlet fever) and on development of post-streptococcal sequelae. In *Proceedings of the Second Clinical ACTH Conference.* Vol. I. 531 pp. Edited by J. R. Mote. Philadelphia: Blakiston, 1951. Pp. 486-496.

12. Mirick, G. S. Effects of ACTH and cortisone on antibodies in human beings. *Bull. Johns Hopkins Hosp.* **88**:332-351, 1951.

13. Bjørneboe, M., Fischel, E. E., and Stoerk, H. C. Effect of cortisone and adrenocorticotrophic hormone on concentration of circulating antibody. *J. Exper. Med.* **93**:37-48, 1951.

14. Germuth, F. G., Jr., Oyama, J., and Ottinger, B. Mechanism of action of 17-hydroxy-11-dehydrocorticosterone (compound E) and adrenocorticotropic hormone in experimental hypersensitivity in rabbits. *J. Exper. Med.* **94**:139-170, 1951.

15. Long, J. B., and Favour, C. B. Ability of ACTH and cortisone to alter delayed type bacterial hypersensitivity. *Bull. Johns Hopkins Hosp.* **87**:186-202, 1950.

16. Fischel, E. E. Hypersensitivity and hyperadrenal state. In *Transactions of the Third Conference on Connective Tissues.* 204 pp. Edited by C. Ragan. New York: Josiah Macy, Jr., Foundation, 1952. Pp. 117-166.

17. Loveless, M. H. Influence of ACTH on sensitizing and immunizing antibodies of inhalant allergy. *Bull. New York Acad. Med.* **27**: 495-509, 1951.

18. Schwab, L., et al. Experimental hypersensitivity in rabbit: effect of inhibition of antibody formation by x-radiation and nitrogen mustards on histologic and serologic sequences, and on behavior of serum complement, following single large injections of foreign proteins. *J. Exper. Med.* **91**:505-526, 1950.

19. Hektoen, L., and Corper, H. J. Effect of mustard gas (dichloroethylsulfid) on antibody formation. *J. Infect. Dis.* **28**:279-285, 1921.

20. Gilman, A., and Philips, F. S. Biological actions and therapeutic applications of B-chloroethyl amines and sulfides. *Science* **103**: 409-415, 1946.

21. Philips, F. S., Hopkins, F. H., and Freeman, M. L. H. Effect of tris (beta-chloroethyl) amine on antibody-production in goats. *J. Immunol.* **55**:289-296, 1947.

22. Spurr, C. L. Influence of nitrogen mustards on antibody response. *Proc. Soc. Exper. Biol. & Med.* **64**:259-261, 1947.

23. Jimenez Diaz, C., Arjona, E., Ales, J. M., Segovia, J. M., and Perianes, J. Effecto de li mostaza nitrogenado sobre la formación de anticuerpos. *Rev. clin. espan.* **43**:203, 1951.

24. Taliaferro, W. H., and Taliaferro, L. G. Effect of x-rays on immunity: review. *J. Immunol.* **66**:181-212, 1951.

25. Dixon, F. J., Talmage, D. W., and Maurer, P. H. Radiosensitive and radioresistant phases in antibody response. *J. Immunol.* **68**: 693-700, 1952.

26. Jacobson, L. O., Robson, M. E., Marks, E. K., and Goldman, M. C. Effect of irradiation on antibody formation. *J. Lab. & Clin. Med.* **34**:1612, 1949.

27. Hoster, H. A., Dratman, M. B., Craver, L. F., and Rolnick, H. A. Hodgkin's disease, 1832-1947. *Cancer Research* **8**:1-48 and 49-78, 1948.

28. Pullinger, B. D. Histology and histogenesis. In *Ross Research on Lymphadenoma.* Edited by T. Horder. 140 pp. Bristol, England: Wright, 1932. Pp. 117-136.

29. Schier, W. W. Unpublished data.

MANAGEMENT OF THE AMBULATORY DIABETIC PATIENT*

JOHN W. RUNYAN, JR., M.D.,† AND DAVID HURWITZ, M.D.‡

ALBANY, NEW YORK, AND BOSTON, MASSACHUSETTS

WITH the large and ever-increasing diabetic population, it is essential for all physicians to have a working knowledge of the diagnosis and treatment of this disease. Since we are convinced that the diagnosis and management of newly discovered diabetes should be conducted on an ambulatory basis, this paper describes a method used in a large outpatient clinic that can readily be adapted to the handling of private patients.

A person with newly discovered diabetes who is told that hospitalization is necessary becomes unduly alarmed about the gravity of his disease. If regulated in the hospital, the regimen often requires major adjustments when he resumes normal activity at home. The shortage and expense of hospital beds constitute a deterrent to hospitalization. If the patient can continue to work while his diabetes is being controlled the cost is reduced, and, more important, he is assured that his condition can be readily controlled by his own physician. Hospitalization should therefore be reserved for patients who are in acidosis or who have other serious complications.

DIAGNOSIS

The diagnosis should be made within the first two visits. A patient who has symptoms such as thirst, polyuria, pruritus, fatigue and weight loss and who is found to have a large amount of sugar in the urine is almost surely diabetic. As in all cases of suspected diabetes, a test for blood sugar should be made at the first visit. A determination two or three hours after a meal is preferable to a fasting specimen and is often diagnostic. When the initial blood sugar level does not conclusively indicate diabetes a second specimen is taken two hours after a meal high in carbohydrate (50 to 100 gm.) on the second visit. The diagnosis of diabetes can usually be confirmed or excluded by the second determination. The diet should not be restricted between the first and second specimens. The figures used as a guide for this purpose are presented in Table 1.

TABLE 1. *Blood Sugar Levels Two Hours after a High-Carbohydrate Meal.*

DIAGNOSTIC CONCLUSION	LEVEL BY FOLIN-WU METHOD (VENOUS BLOOD)	LEVEL BY SOMOGYI-NELSON METHOD* (VENOUS BLOOD)
	mg./100 cc.	*mg./100 cc.*
Diabetes present	161 or over	151 or over
Diabetes excluded	120 or less	100 or less
Further study indicated	121-160	101-150

*So-called true-glucose method.

Further study is only rarely necessary to establish or to exclude the diagnosis of diabetes. The glucose tolerance test remains the only satisfactory method for this purpose. We have used the standard oral technic, which consists of the administration of 100 gm. of glucose to the fasting patient, who has been on a full, unrestricted diet, including

*From the Diabetes Service, Boston City Hospital, and the Diabetes Section, United States Public Health Service.

†Instructor in medicine, Albany Medical College; clinical director, Albany Medical Center Clinics, Albany Hospital; formerly, research associate, Harvard Medical School, and research fellow in medicine, Thorndike Memorial Laboratory, Boston City Hospital; formerly, senior assistant surgeon (R), United States Public Health Service.

‡Clinical associate in medicine, Harvard Medical School; chief, Diabetes Service, Boston City Hospital; chief of medicine, Mount Auburn Hospital, Cambridge; consultant, Diabetes Section, United States Public Health Service.

sweets, for two or three days before the test. Fasting, one-hour, two-hour and three-hour specimens of blood and urine are collected. By the present criteria of interpretation a definite diagnosis of diabetes is made in patients whose blood sugar is high at two hours and does not fall below 120 mg. per 100 cc. by the Folin–Wu method or 100 mg. per 100 cc. by the Somogyi–Nelson method at the end of three hours. Patients with borderline levels are followed at intervals. Mildly positive or equivocal tests obtained during pregnancy, infections and hyperthyroidism should be repeated at a later date.

Treatment

In the past hospitalization of patients with newly discovered diabetes has been considered necessary primarily for two reasons: dietetic training, which most physicians are not prepared to give in the detail necessary for a diabetic patient, and instruction in the use of insulin. Actually both types of instruction can readily be given by the doctor in his own office or in the clinic setting.

Diet

Diet should be chosen to give the patient the optimal intake for his body build and energy needs. This should conform as closely as possible to his normal requirements and eating habits. The use of special foods, such as gluten bread and diabetic desserts, is not advised. We have found the *Meal Planning Booklet** of great help to the physician and patient in planning diets. It is simple and graphic. This diet system presents six basic meal plans varying from 1200 to 2600 calories. For simplification, all foods are arranged in six groups or exchanges. The portions of food in each list are based on common household measurements, which have been found to be satisfactory for clinical use. Weighing of foods is eliminated entirely. The carbohydrate, protein and fat composition of the sample meal plans (Table 2) is based on common eating practices.

When the requirements of the patient deviate considerably from these sample meal plans the diet may be easily arranged to meet particular needs by the use of the six food exchanges; this is true, for example, of the diabetic patient on a peptic-ulcer regimen or one requiring more than 2600 calories.

Table 2. *Sample Meal Plan (1800 Calories).*

Meal	Exchanges and Amount	Example and Measure	Composition			
			Carbohydrate	Protein	Fat	Calories
Breakfast	1 fruit	Prunes — 2 (medium size)	10	—	—	40
	1 meat	Egg — 1	—	7	5	73
	2 bread	Toast — 2	30	4	—	136
	2 fat	Butter — 2 teaspoonfuls	—	—	10	90
	Coffee or tea (any amount)		—	—	—	—
	Totals		40	11	15	339
Lunch	2 meat	Ham & cheese sandwich (cheese, 1 oz.; ham, 1 oz.)	—	14	10	146
	2 bread	2 slices	30	4	—	136
	Vegetable (List 2A)	Lettuce & tomato salad (any amount)	—	—	—	—
	1 fruit	Apple, 1 small	10	—	—	40
	1 milk	Whole milk — 1 cupful	12	8	10	170
	1 fat	Butter — 1 teaspoonful	—	—	5	45
	Coffee or tea (any amount)		—	—	—	—
	Totals		52	26	25	537
Dinner	3 meat	Hamburg patties — 3 oz.	—	21	15	219
	2 bread	Mashed potato — ½ cupful Bread — 1 slice	30	4	—	136
	Vegetable (List 2A)	Spinach (any amount)	—	—	—	—
	1 vegetable (List 2B)	Carrots — ½ cupful	7	2	—	36
	1 fruit	Banana — ½ (small)	10	—	—	40
	2 fat	Butter — 2 teaspoonfuls	—	—	10	90
	Coffee or tea (any amount)		—	—	—	—
	Totals		47	27	25	521
Bedtime	1 milk	Whole milk — 1 cupful	12	8	10	170
	2 bread	Soda crackers — 6	30	4	—	136
	1 meat	Peanut butter — 2 tablespoonfuls	—	7	5	73
	Totals		42	19	15	379
	Grand totals		181	83	80	1776

The physician should familiarize himself with the *Meal Planning Booklet* and also with the *Diabetic Diet Card for Physicians*, which is simple and brief and can be obtained from the same source. Instruction to the patient in the use of the meal-planning booklet is essential. It is preferable to extend these instructions over several short sessions, rather than to give them at a single session. It is necessary to review the diet with the patient from time to time to evaluate his understanding of the material and to make any necessary adjustments.

Insulin

In general all patients with frank symptoms of diabetes should immediately be started on insulin. Details of its use in various types of diabetes are given in the final section of this article. Usually, within twenty-four hours of the first injection,

*Prepared by the American Diabetes Association, the American Dietetic Association and the United States Public Health Service, Diabetes Section. Copies may be obtained at low cost from Health Publications Institute, Raleigh, North Carolina.

thirst, polyuria and nocturia will have abated, demonstrating to the patient the benefits of insulin. Psychologically, it is also better for the patient to be told that the amount of insulin needed may later be decreased or even omitted (this is true in obese and elderly patients, not the young ones) than to find it necessary to begin insulin after failure with diet alone. The initial injection may be given at any time during the day, but subsequently the insulin should be administered at the same time each day — just before breakfast. Insulin given at other times during the day is to be avoided if possible.

Types of insulin. The use of NPH insulin has steadily increased. It has largely replaced protamine zinc insulin in our experience, and all new patients requiring insulin are given NPH. The action usually begins within four or five hours and reaches its peak in eight to ten hours, lasting for about twenty to twenty-four hours. Its advantages over protamine zinc insulin are as follows: quicker effect, regular insulin may be added to it without loss of the rapid action of regular insulin and reactions are more likely to occur during waking hours and can be effectively prevented by appropriately timed feeding.

Protamine zinc insulin, a widely used, slowly-acting form, is still being given to patients who have been well regulated on it and who are reluctant to change. It has a slower onset of action than NPH and cannot be used as well in mixtures because the excess protamine present combines with the regular insulin.

Regular or crystalline insulin is a quick-acting type whose effect is over in four to six hours in ordinary dosages. It is primarily used in conjunction with the slow-acting insulins and in diabetic acidosis.

Technic of administration. After the decision is made that insulin is necessary, it should be given immediately. The patient is instructed to hold the syringe, which is loaded with insulin, as if it were a pencil. The skin of the leg is prepared with alcohol and held taut by the physician, and, while he steadies the patient's hand, the needle is inserted perpendicularly to its hilt. After the needle has penetrated the surface of the skin, it is, of course, painless, and this should be pointed out. The patient is then told to push the plunger down and is allowed to pull out the needle and syringe. He gains confidence after he learns that the injection is a simple, practically painless procedure. He is more relaxed and may then be instructed in the sterilization of the equipment, the withdrawing of insulin from the bottle and so forth. Local skin reactions are extremely rare when the insulin is given deep in the skin by means of a 1-cm. No. 26 needle inserted at right angles.

Control

Frequent urine testing for sugar by the patient (usually three or four times daily on specimens excreted before meals) is advised while the disease is being controlled. The patient should keep a written record of the tests. As the diabetes becomes better controlled, less frequent testing is necessary.

Since complications involving the feet account for a large portion of hospitalization and disability, instruction in the proper care of the feet is of considerable importance. Instructions should be given, and possible sites of trouble pointed out, when the feet are inspected. Epidermophytosis, which is frequently encountered, usually responds to any of the commercially available undecylenic acid preparations.

After the initial instructions the patient is checked daily for a few days to ascertain how well he has progressed with the diet and insulin administration. Less frequent visits are then necessary for adjustment of insulin and diet. Satisfactory regulation can usually be accomplished within one to three weeks.

In controlling young and middle-aged patients, we attempt to keep the urine specimens taken before meals as nearly sugar free as possible without provoking hypoglycemia. This can be effected in the stable form of the disease with blood sugar levels close to normal. In the labile form control is more difficult, and the patient may have incapacitating hypoglycemic reactions. The urine of the elderly diabetic patient on insulin should not be kept absolutely free of glucose. The blood sample taken after meals has the distinct advantage over the fasting specimen in that there is no disruption in the usual time for breakfast and insulin.

Clinical Types of Diabetes

The Obese Patient

The obese patient is the most frequently encountered type. Characteristically, the diabetes is relatively stable, and insulin reactions and acidosis seldom occur.

Dietary patterns in the obese patient generally need altering. Diets varying from 1200 to 1800 calories are usually prescribed. However, too drastic restrictions in food intake may result in the discouragement and a possible total disregard of the diet. For example, patients engaged in heavy labor, whose food intake has been 4000 to 6000 calories, can lose weight on a prescribed diet of 2000 to 2600 calories. By prescribing a realistic diet and maintaining an interest in the patient and his problems, one can accomplish weight reduction. A persistant problem is the maintenance of weight reduction after it is once achieved.

The obese patient with symptoms of diabetes is started on 10 to 20 units of NPH insulin initially. Increases of 5 to 10 units every two to seven days are made until adequate control has been accomplished. If weight is reduced insulin can often be discontinued after several months. In the asympto-

matic obese patient, in spite of an initial high blood sugar level, insulin is usually unnecessary if significant weight reduction takes place.

The Middle-Aged Patient of Normal Weight

Some middle-aged patients of normal weight may have the characteristics of the juvenile patient in that the blood sugar is labile, but in others the diabetes is quite stable.

The patient with symptoms is started on 15 to 20 units of NPH insulin. Increases of 5 to 10 units every two to four days are made until the disease is satisfactorily controlled. Since it is usually not advisable to reduce the food intake in these cases it is preferable to begin with a small dose of insulin, even when the patient is asymptomatic, if there is moderate glycosuria and blood sugar levels are elevated.

The purpose of a diet in these patients is to maintain a relatively constant food intake from day to day and to prevent both significant gains and losses in weight. The diet prescribed is based on, and should closely approximate, previous food intake. Diets of 1500 to 2200 calories are usually prescribed, but diets of 2600 calories and above are occasionally necessary. Adjustments in the diet must be made from time to time.

The Elderly Patient

The elderly patient characteristically has mild diabetes and the type of regimen is planned on an individual basis. However, if the patient is having definite symptoms, a small dose (10 to 15 units) of NPH insulin should be given initially. It may be necessary to increase this dosage at intervals to decrease the amount of glycosuria. If an elderly patient continues to show a large amount of glycosuria and persistently high blood sugar levels but denies symptoms, a small dose of long-acting insulin should be started. Insulin can frequently be stopped after a few months.

It is in the elderly patient that high blood sugar levels, with minimal or no glycosuria often occur. The ambulatory patient exhibiting such findings is usually asymptomatic. It is believed that insulin therapy is not indicated in such cases, unless glycosuria develops or infection intervenes.

Alterations in the patient's eating habits should, as a rule, be minimal, provided the food intake has been well balanced in the past. Idiosyncrasies should be corrected. Slight to moderate restrictions in food intake are often well received. This restriction should be no greater than necessary to maintain a normal weight. Weight reduction is seldom a problem in the elderly patient.

The Juvenile Patient

The first few interviews are most important in establishing rapport in these cases. The attitudes developed toward the disease depend, to a great extent, on how the problem is presented. It is just as important to stress the positive as the negative aspects. Therefore, in becoming acquainted with the juvenile patient, one should stress the fact that he may continue to participate in sports and other activities as in the past. Responsibility for the day-to-day care of the diabetes is shared by the parent (usually the mother) and the patient. However, as much responsibility for this care as his maturity warrants should be assumed by the patient. Although both patient and parent should be acquainted with the technic of insulin administration the patient himself should be responsible for daily administration unless he is ill. This sharing of responsibility is also true of urine tests and diet, even though the actual preparation of meals is done by the parent. If instruction is presented in such a way that the primary responsibility for the care of the diabetes rests with the patient himself, if the positive approach is emphasized and if an adequate food intake is prescribed, the resentments and negativism that often arise in the juvenile patient can be kept to a minimum.

The disease in these cases is characteristically labile, and insulin is invariably required for control. It is not advisable to attempt control with diet alone even in the rare case without symptoms. The caloric needs of the growing patient must be met, and this is not possible without insulin.

As soon as the diagnosis has been established by laboratory and clinical means, treatment should be instituted. In general, at least one blood sugar determination should be reported before treatment is started. However, it is justifiable to begin therapy without the blood sugar report when there is clear clinical evidence of diabetes, together with a strongly positive urine test for sugar. A delay in instituting therapy may permit acidosis to develop.

The blood sugar level is not usually a helpful gauge to the initial insulin dosage required. When there are frank symptoms of diabetes (but not diabetic acidosis),* which are usually present in juvenile patients, the initial dose may be 20 to 30 units of NPH insulin if the child is ten years of age or older. Younger children should be given proportionately smaller doses. Adjustments are then made in the daily dose of NPH insulin by frequent visits to the physician until an adequate degree of control is established. Usually, increases do not exceed 5 to 10 units every one to three days unless it is evident by the appearance of acetone and continual ++++ tests for sugar in the urine that a larger amount of insulin is necessary. As the patient and parent develop skill in adjusting the daily insulin dosage, the frequency of visits to the physician may be safely reduced.

Although the majority of juvenile patients can be controlled with a single dose of NPH insulin

*Patients in diabetic acidosis and those who have been vomiting should be admitted to the hospital.

before breakfast, some need additional regular insulin. This can be added directly to the NPH in the mornings to control late-morning glycosuria. Occasionally, regular or NPH insulin is necessary at other times during the day. Rarely, control may be more satisfactorily obtained with combinations of protamine zinc and regular insulin than with NPH insulin.

Modifications in eating patterns are usually necessary for satisfactory control. Meals and feedings should be at the same time each day, although these times and the number of feedings may vary from patient to patient. Intake of calories should be sufficient, so that the patient never feels hungry and so that a steady weight gain is possible. In this way many of the emotional conflicts can be minimized. A diet containing less than 2200 calories is seldom prescribed, 2600 to 3400 calories frequently being necessary. The divisions into carbohydrate, protein and fat are those that would naturally be found in a well balanced diet. After the initial diet plan has been presented adjustments are necessary, depending on the rate of weight gain, the occurrence of insulin reactions and the patient's desires. An erratic intake of concentrated sweets should be avoided. However, if the patient is unwilling to accept this denial as indicated by repeated indulgence, it is better to work a given amount into the diet each day rather than to allow the point to become an issue. Routinely, juvenile patients taking NPH insulin receive 3 meals a day in addition to an afternoon (at 2:00 to 3:00 o'clock) and an evening feeding (at 8:30 to 10:00 o'clock). Occasionally, a mid-morning feeding is indicated if late-morning reactions develop.

Discussion

Insulin reactions occur more frequently in the labile form than in any other type of diabetes. Special efforts should be made to determine the circumstances leading to hypoglycemic episodes, with the purpose of preventing them in the future. This is often successful. An unusual expenditure of energy, as in sports or work during the previous twenty-four hours, failure to eat at the usual time, failure to eat the usual amounts, insulin injection at an unusual time during the day and emotional instability are the more common factors responsible for precipitating hypoglycemic episodes. It is usually advisable for patients who are subject to reactions to take an additional feeding before or during participation in excessive physical activity. Recurrent reactions at a particular period during the day can be avoided by a change in the time of a feeding or by the addition of a feeding half an hour to an hour before the expected time of the reaction.

The diabetic patient in any age group who is underweight and malnourished as a result of uncontrolled disease, previous drastic dietary restrictions or other circumstances needs a food intake sufficient to restore his weight to normal. Nourishment between meals, in addition to full meals, is indicated. The total calories prescribed may be from 3000 to 3600. Insulin is invariably needed under such circumstances. After there has been a satisfactory regain of weight, a downward adjustment in calories is indicated. Diabetic patients with cirrhosis should receive a high-calorie intake and sufficient insulin to control the diabetes.

The patient with angina pectoris and uncontrolled diabetes may be dramatically benefited by effective therapy. Insulin may be given to such patients, but hypoglycemia should be avoided.

Summary and Conclusion

An outline for the management of the diabetic patient in the clinic or office on an ambulatory basis is presented.

Medical, psychologic and economic considerations make this method preferable to routine hospitalization of the patient with uncontrolled disease.

CORTISONE AND ACTH IN PREGNANCY*

LAWRENCE KATZENSTEIN, M.D.,† AND ALLSTON N. MORRIS, M.D.‡

WILMINGTON, DELAWARE

EXPERIMENTAL evidence suggests that the administration of cortisone and ACTH to animals during pregnancy may be dangerous to the fetus. Yet, in the few cases in which this therapy has been given to pregnant women, there has been no harm to the offspring. Because of this apparent contradiction, the following case of dermatitis herpetiformis of pregnancy, treated for six months with cortisone and ACTH, with delivery of a normal baby, is presented.

CASE REPORT

T. H., a 36-year-old woman, was first seen on February 18. 1952, complaining of an itching eruption of the arms and legs of about 1 week's duration. She was in the 3d month of her 2d pregnancy.

The past history revealed no significant illnesses and no previous skin eruption.

The positive physical findings, aside from those of pregnancy, were limited to the extremities, which disclosed a widespread excoriated eruption. The lesions were grouped, with both an urticarial and eczematous component. Severe edema of the feet and lower legs was present even though the eruption was not grossly infected. The mucous membranes showed no lesions.

A tentative diagnosis of dermatitis herpetiformis of pregnancy was made, and therapy with 4 gm. of sulfapyridine daily was started. Within the next 2 weeks, despite this treatment, bullae appeared in the involved areas, and the pruritus became so intense that the patient was admitted to the hospital on March 10.

Laboratory studies showed a normal blood count and urine. The serologic test for syphilis was negative. A biopsy of a bulla was diagnosed as "compatible with dermatitis herpetiformis." Therapy was started with Roniacol Tartrate, 50 mg. 4 times daily, but there was no improvement. The pruritus was so severe that large doses of sedatives were needed. New bullae continued to appear, being most numerous on the legs. These were ruptured by excoriation, leaving large denuded areas. The patient's condition deteriorated quickly so that interruption of the pregnancy was considered. Finally, it was decided that a trial of steroid therapy was indicated, even though there were misgivings about its effect on the 4-month fetus.

Treatment was started on March 15 with intravenous injections of ACTH, 20 mg. in 1 liter of 5 per cent glucose in water, given daily over a period of 8 hours. After the 1st day there was much less itching, and after 3 days no new bullae appeared. On the 5th day of therapy the ACTH was stopped, and 175 mg. of cortisone given by mouth. During the reminder of the hospital course the cortisone dosage was gradually reduced until discharge on March 26 on a dose of 62.5 mg. daily. At this time there was no itching and no new bullae, and the eruption was involuting.

About 6 weeks after discharge, 100 mg. of cortisone daily was necessary to prevent the development of new bullae, but this dose caused marked edema of the legs. Accordingly, the drug was stopped, and Acthar Gel, 40 mg. daily, was given. It was continued in gradually diminishing amount and frequency and finally could be stopped just 2 weeks before delivery. From the 4th to the 9th month of pregnancy the patient received approximately 3.0 gm. of cortisone and 1.3 gm. of ACTH.

On September 4 a normal male infant, weighing 5 pounds, 2 ounces, was delivered. At birth physical examination revealed no abnormalities. Since then, the child has had a normal growth and development.

*From the departments of Dermatology and Medicine, Delaware Hospital.

†Attending chief, Department of Dermatology, Delaware Hospital.

‡Assistant in medicine, Delaware Hospital.

DISCUSSION

As noted above, there is experimental evidence that the administration of cortisone and ACTH during pregnancy may be dangerous to the fetus. An editorial[1] refers to the work of Fraser and his associates,[2, 3] who produced anomalies in fetal mice by giving cortisone daily for four days at various stages of pregnancy. When the dose was lowered to 0.625 mg. no anomalies occurred; nor did they occur in untreated controls. It was pointed out that comparable dosage on a weight basis in human beings would be 2.0 to 8.0 gm. daily. Courrier[4] gave pregnant rabbits 25 mg. of cortisone daily for four to seven days and found the fetuses to be small, resorbed or macerated. Glaubach, Antopol and Graff[5] reported dead fetuses or death on the second to the fifth day of life when pregnant mice were given 2.5 mg. of cortisone for two to eight days before parturition. And Robson and Sharaf,[6] who also worked with pregnant mice, stated that pregnancy could be interrupted by both cortisone and ACTH.

Despite the adverse effect on the offspring when steroids are given experimentally to pregnant animals, we could find no report of damage to a baby from steroid therapy administered to pregnant women. Singh et al.[7] described a twenty-one-year-old Negress with acute rheumatic fever who was given ACTH over a seventeen-day period (total of approximately 1200 mg.) in the last month of pregnancy, with no resultant harm to the fetus. Two women with pemphigus[8, 9] were treated with cortisone and ACTH during pregnancy, with delivery of normal children.

Doerner et al.[10] report on the administration of cortisone to 2 sensitized Rh-negative pregnant women in an effort to avoid erythroblastosis fetalis. One fetus was stillborn, with hydrops fetalis. The other, whose mother was given approximately 2600 mg. of cortisone in the last five weeks of pregnancy, was born with clinical erythroblastosis fetalis and survived. Anderson, Barr and Slessor[11] report another case in which the second child had died of erythroblastosis fetalis. During the third pregnancy the patient received 100 mg. of cortisone daily from the thirty-third to the thirty-seventh week. This child had mild erythroblastosis at birth, but the authors believed that no adverse effect had been demonstrated on mother or fetus. Finally Kline and his associates[12] described a woman with pulmonary berylliosis who was given ACTH at the beginning of her second pregnancy and cortisone during the last eighty-seven days of the pregnancy. She was delivered of an apparently normal child

in whom severe hypoglycemia developed forty-eight hours after delivery. The child was treated with fluids and cortisone and was discharged from the hospital eleven days after birth, apparently normal.

Thus, there are reports, including the one presented above, of 8 women who have received clinically significant amounts of ACTH or cortisone, or both, during pregnancy without untoward effect on the fetus. In the light of the experimental evidence that the exhibition of steroids during pregnancy is not without grave danger to the fetus, many more cases will have to be accumulated before the clinician can feel entirely safe in using these drugs.

One can only suggest the possible reasons why the clinical results of steroid administration during pregnancy are not so dire as those suggested by the experimental work: too few cases have been reported; the dosage given, which, on a weight basis, has been much smaller than that in the experimental work; species differences; the time during pregnancy when the drugs have been given. At present the difference in dosage appears to be the most valid reason.

Summary

A case of dermatitis herpetiformis of pregnancy treated with ACTH and cortisone, with birth of a normal baby, is presented.

Seven other cases of normal births after therapy with steroid hormones during pregnancy are reviewed.

Despite contradictory experimental evidence, the few clinical reports collected suggest that steroid therapy during pregnancy results in no damage to the infant.

References

1. Editorial. Experimental production of congenital anomalies with cortisone. *J. A. M. A.* **148**:206, 1952.
2. Fraser, F. C. Experimental production of congenital anomalies. *Canad. M. A. J.* **64**:270, 1951.
3. Fraser, F. C., and Fainstat, T. D. Production of congenital defects in offspring of pregnant mice treated with cortisone. *Pediatrics* **8**: 527-533, 1951.
4. Foreign Letter. Cortisone and gestation. *J. A. M. A.* **146**:493, 1951.
5. Glaubach, S., Antopol, W., and Graff, S. Excessive doses of cortisone in pregnant mice: effect on development and survival of fetus and newborn and on maternal breast tissue. *Bull. New York Acad. Med.* **27**:398, 1951.
6. Robson, J. M., and Sharaf, A. A. Interruption of pregnancy with ACTH and cortisone. *J. Physiol.* **114**:11P, 1951.
7. Singh, B. P., and Miller, L. F. Effect of ACTH on acute rheumatic fever in pregnancy. *Am. J. Obst. & Gynec.* **63**:452-454, 1952.
8. Samitz, M. H., and Wiggall, R. H. Pemphigus vulgaris, cortisone therapy. *Arch. Dermat. & Syph.* **64**:379, 1951.
9. Samitz, M. H., Greenberg, M. S., and Coletti, J. M. Pemphigus in association with pregnancy: observations on effect of corticotropin (ACTH) and cortisone on pemphigus, pregnancy and infant. *Arch. Dermat. & Syph.* **67**:10-17, 1953.
10. Doerner, A. A., Naegele, C. F., Regan, F. D., Shanaphy, J. F., and Edwards, W. B. Effect of cortisone on sensitized Rh-negative pregnant women and an erythroblastotic infant. *J. A. M. A.* **147**: 1099-1101, 1951.
11. Anderson, J. R., Barr, G. M., and Slessor, A. Attempt to prevent erythroblastosis foetalis by use of cortisone during pregnancy. *Brit. M. J.* **2**:542-544, 1952.
12. Kline, E. M., Inkley, S. R., and Pritchard, W. H. Five cases from fluorescent lamp industry: treatment of chronic beryllium poisoning with ACTH and cortisone. *Arch. Indust. Hyg.* **3**:549-564, 1951.

SPECIAL ARTICLE

THE USE OF COMMUNITY MEDICAL RESOURCES*

Henry F. Howe, M.D.†

COHASSET, MASSACHUSETTS

THE establishment of a medical practice presents countless needs for learning legal and quasi-official technics that were taken care of without effort while the physician was still an intern. He is required to fill out not only birth certificates and death certificates but also serologic reports for marriage and pregnancy, reports on contagious diseases, proofs of death, forms for accident and health insurance, Blue Shield applications and many varieties of physical-examination blanks for insurance or employment. He certifies illnesses of employees, vaccinations of school children and gunshot wounds for the police. He must learn which deaths to refer to the medical examiner or coroner, which charity cases to the public welfare board or Veterans Administration, and which child or senile patient to Aid to Dependent Children or Old Age Assistance. There are reports of industo comply with and committals of the insane to process. He gradually learns that he must keep on his cess. He gradually learns that he must keep on his shelves up-to-date copies of the manuals of procedure of the state department of health, the Veterans Administration and Blue Shield. He must know the United States State Department's requirements for immunizations of travelers to foreign countries. He must learn where to refer sick military personnel and how to refer parents to a good adoption agency.

Modern civilization, especially modern government, has filled the physician's life with the irritating details of such paper work. The fact should not be lost sight of, however, that these tedious technics often enable the physician to solve difficult problems by means that were not available to him a generation ago, and also to handle a volume of social questions that he could not have encompassed by the hit-or-

*Adapted from a chapter entitled "The Use of Community Medical Resources" in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publisher, Little, Brown & Company, Boston.

†Medical examiner, Second District, Norfolk County; formerly, president, Norfolk South District Medical Society.

miss methods of the "good old days." Many of these forms and blanks represent easy solutions (provided by the Government or insurance companies) of problems that the unaided physician used to take care of inadequately through charities that he often had to dream up himself or supply from poor community resources. This process has removed from the physician much of the burden of improvising care for the poor.

Other technics are actually those of preventive medicine: immunizations, reports of industrial accidents and venereal and contagious disease procedures, as well as compulsory serologic tests. The police, psychiatric and medicolegal technics, so far as they serve the public safety, are likewise preventive medicine in the broadest sense.

Different states and communities vary widely in the degree of development and methods of handling of such administrative matters. There is therefore nothing to be gained by a detailed account of procedure. It is of the utmost importance, however, for the physician to make his own study of all available community resources in his particular area and thus to familiarize himself with the orderly procedures required by each agency concerned. His secretary should be trained to take much of the detailed paper work off his shoulders as time goes on, but the doctor himself must thoroughly understand the technics involved. The public will measure him as shrewdly by his ready use of these tools as by his handling of disease. Insurance, employment and public safety are all a part of the medical problem from the patient's point of view. The family of the insane, the aged, the worker in industry or the chronically ill judge their physician as much by his adeptness in handling the economic factor as by his clinical competence. His expression of annoyance at filling out a paper is interpreted as lack of interest in their problem.

If this is true of the mere matter of paper work, how much more is it true of the use of the more individualized social and professional agencies of a particular region! Most communities have their own special arrangements about ambulance service, oxygen therapy, state-supplied vaccines, tests for pregnancy and Rh factor, hearing-aid clinics, remedial reading and chest x-ray services. Some of these may be afforded very simply by the hospital. But, if not it is the physician's responsibility to know how to obtain them with most consideration for the patient's pocketbook. Needy patients should not be denied such services if they are obtainable through public funds or private charitable agencies. People of moderate means should not be sent to a more expensive source if a competent, inexpensive one is ethically available. Such full information is a part of the physician's armamentarium. No needy patient forgives him for hiring a private ambulance if a good police ambulance is available to every citizen.

By the same token accurate information about the proper use of both public and private agencies for the diagnosis and care of chronic illness is essential. In the fields of tuberculosis, cancer, diabetes, arthritis, heart disease, poliomyelitis and rehabilitation many states now have public or endowed foundations for cushioning the economic disaster of these prolonged disabilities. There are few people so prosperous as not to need this help. It has become a part of the doctor's function to co-operate with these organizations in the referral and follow-up care of such cases. It is short-sighted to allow a family to spend itself into bankruptcy in private care of such situations when adequate facilities are available at less cost. When people are put out of action in the combat of life, a good chain of evacuation affords the only chance for a patient to "live to fight another day." Piling complete economic catastrophe on top of partial physical disaster often allows little on which to build later rehabilitation. The practitioner sometimes holds this choice in his hands in his management of prolonged illness. The large teaching hospital in which the young physician was trained had social workers whose career was spent in the study and policy determination of such problems; in private practice, the physician is often necessarily his own social worker.

The same principle applies to the use of convalescent and nursing homes as contrasted on the one hand with hospital care and on the other with special nursing in the patient's home. A physician should inspect the convalescent and nursing homes in his region and become familiar with the competence of their nursing staffs and with the way to allocate patients to them with some regard to the kind of care they are going to get in each. Similarly, he should learn all he can about the availability of good household or partially trained nurses for home care of disabled or aged patients. His hospital he necessarily knows, but he should possess first-hand knowledge about the available alternatives to hospital care in chronic illness. Where can the hemiplegic patient get really rehabilitating care? Where can the orthopedic patient get physiotherapy? At what point must the senile person be committed to a psychiatric ward? Where can the patient with terminal cancer most happily live out his last days?

Consideration should be given to the choice and use of nurses. Certain physicians have a bad reputation among nurses, usually for attaching blame to them when it is undeserved. Either the physician is so vague in giving orders that whatever the nurse does turns out to be wrong or he is so rigid in his requirements that the nurse is afraid to adapt the orders to the real situation. Every physician should regard the nurse as a member of an allied profession that has its own standards of conduct and procedure beyond which she cannot be expected to go. He cannot fairly ask her to diagnose or to carry out treat-

ment without specific orders. So-called standing orders are of doubtful validity unless the doctor periodically checks the patient and confirms such orders to the nurse. Yet because of her watchfulness the nurse's judgment about alarming or unusual symptoms can be of great help to the physician, and her warning in their incipiency often saves him from the embarrassment of overlooking serious complications. A doctor who closes his ears to such suggestions or brushes them off impatiently is not making full use of his resources. The skillful physician learns to evaluate the individual capacities of his nurses and apply principles of personnel management to the placement, especially for private duty, of certain nurses in certain types of cases or in certain personality problems among his patients. No medicine or regimen of treatment can approach in effectiveness the proper choice of the right nurse for the particular patient. And nothing can so ensure the continuity of effective relations as expressions of appreciation of the nurse when her work deserves them. By the same token, she should not be reprimanded in the patient's presence any more than one would reprimand another physician in the same circumstances. Good care of the patient requires the confidence that only mutual courtesy can provide.

Since all nurses do not have the same capacities part of the doctor's job is to allocate responsibility to a nurse only as her training and talents justify it. Some good ward administrators lack the personal touch for the home. Surgical nurses are hardly at ease with the prolonged disability of an arthritic patient. Elderly patients often require a nurse who is self contained, not talkative. It is therefore advisable for a physician to keep a list or card file of nurses for special assignments in private duty. This is particularly desirable among partly trained or attendant or practical nurses, whose degree of education and professional judgment is so variable as to be undetermined except through previous experience. The degree of rehabilitation in prolonged or chronic illness sometimes depends almost wholly on the ability of the physician to choose an intelligent, willing attendant and train her on the job. A card index in the doctor's own office can be a more fruitful resource than a nurses' registry in the obtaining of such invaluable attendant service, though the registries themselves often make excellent assignments.

The problem of the use of community resources is in essence one of referral. Thus far I have considered chiefly the institutional and public-agency types of referral. No discussion of community resources could be complete, however, without some attention to the choice of medical referrals or consultations. To some this may seem superfluous, since all practitioners build up for themselves a group of specialist consultants of their own choosing, often for quite personal reasons. But if the study of therapeutics is a life-long one, the study of consultation should be of equal duration. The sending of a patient to a consultant is often of quite as momentous significance in the history of an illness as the choice of a drug or of any other treatment. And the availability of good consultants in many fields is a community problem. So also is the manner of consultation.

In group medicine and in hospital practice certain almost inevitable limitations arise in the choice of consultant specialists. A pseudo-business device, the "interdepartmental communication," becomes a habit, and if the staff is large enough, there is still a fairly good selection of men to choose from. But in smaller staffs this device may strictly limit the choice of consultant.

In individual practice the case may be quite different. The young physician may, if he wishes, play the field. He has the whole community or region to choose from. He should try to select consultants so good that their testimony will stand up well in court. He should also pay attention to the technic of consultation. Instead of a consultation request on a hospital record sheet, on which the consultant writes his opinion, the younger doctor more often sends the patient to the office of the chosen consultant. This is a new relation. There are several ways of handling it. He can call up the consultant on the telephone, make the appointment and send the patient along. He can write a few lines on a prescription blank. He can write him a letter. On his choice may depend the effectiveness, or lack of it, of the consultation, unless there is a clear understanding between the two physicians of what is wanted.

Does the referring physician desire a diagnosis, or an opinion, or treatment or moral support? Does he, in sending the patient, expect the consultant to take over care of the illness? Does he need a definite commitment whether the patient should change his job, or go south for the winter? Just what is the question? Should the consultant tell the patient the diagnosis, or is that for the referring physician's ear only? Is the patient supposed to report back to the consultant, or to the referring doctor? Is an insurance question involved? Who should order further studies or x-ray examinations?

Vagueness, both in the request and in the answer to such questions, is responsible for many misunderstandings among physicians and their patients. Without a letter or definite notes made at the time of a telephone conversation, many such consultations go astray and make the patient believe that he has spent a specialist fee for nothing. The fault, which is often twofold, consists of a lack of good technic by both parties. But the failure of technic is not a medical failure so much as it is an administrative one. If a consultation is needed it is worth doing well. Some physicians use a blank form on which pertinent questions are checked off and space is left for the answers. This may seem coldly efficient, but it is useful.

It is by now obvious that many of the problems of wise use of community resources in the practice of medicine are administrative ones. As American society matures, these medical administrative functions in the community tend more and more to become organized in certain patterns of control that may usefully be grouped in two broad classifications. The first of these, which is voluntarily controlled, includes the professional activities of doctors, nurses and hospitals, the business medical arrangements in industry and voluntary insurance, and the charitable medical resources of medical foundations, endowed clinics and public charities. The second is that of governmental health resources, and this, of course, divides itself naturally into municipal, county, state and federal agencies.

This discussion does not concern the political implications of this broad division of health agencies into voluntary versus governmental control; it deals only with the reality as it exists. The young physician has to work with both, and his only concern is the most effective care of the patient, by wise use of all resources available, whatever their origin. It is no service to the patient to deny him the advantage of facilities routinely afforded by government or industry if these are ethically provided.

Thus far some of the professional resources as they concern nurses, nursing homes and specialist consultations have been discussed. Reference has been made to the uses of charitable medical foundations. The functions of industrial medicine and the governmental health resources that any physician necessarily uses must also be considered.

Partly through pressure from insurance companies, and partly because of employers' liability laws, most large industries, banks and commercial houses now maintain medical departments. The trend is spreading rapidly into smaller industries, where facilities for at least part-time coverage by physicians and nurses are becoming common. There are many opportunities in this field for young physicians. But whether a doctor actually draws a retainer from a business organization for part-time or full-time services in industry, he will inevitably treat some industrial cases. It is of the utmost importance that he understand the point of view of industrial or occupational medicine. The chief concern of industry is the prevention of lost time from the job. The injury or illness of skilled workers often seriously retards or stops production and increases insurance costs, besides suspending the income of workers' families. The job of industrial physicians and nurses is not primarily the care of industrial accidents, but rather the prompt return of the worker to useful employment. When the private practitioner is dealing with an industrial case it therefore behooves him to co-operate with this occupational purpose for the good of all concerned. Unnecessarily prolonged convalescence serves no useful purpose. And if during convalescence the attending physician will inquire of the company doctor or nurse whether part time or light work is available for his patient, he will usually earn the gratitude of both the patient and the company doctor. It goes without saying that he should render prompt reports on his patient's progress when they are requested by the company medical department. The industrial clinic is in a sense another community resource that can be used for the better care of the patient if it is realized that the patient's job is one of the tools of medical care. Rehabilitation is not confined to those with amputations but includes every patient with cardiac disease, neurosis or peptic ulcer who loses time from work on account of illness. Most industrial physicians welcome the co-operation of the attending physician in early placement of such patients on light or part-time work as one of the methods of convalescent care. A simple telephone call will usually accomplish this objective. The industrial clinic should be regarded as a beachhead of medical thinking within the productive jungle of industry. The industrial physician speaks the same language as the attending physician. It is easier to talk to him than to the employer.

Governmental health resources are for the most part concerned with public health and public safety. Their demands on the physician in private practice are often those of official duty rather than the immediate care of a patient. The board of health is concerned with sanitation, reports of communicable diseases, testing of water and milk supplies and supervision of food handlers and restaurants. With the co-operation of the school physician, it enforces quarantine, attempts to control epidemics and fosters immunizations. School and public-health nurses furnish health education, social welfare technics and post-partum and child welfare projects. Municipal social workers in many communities handle the disposition of health problems in tuberculosis, old age and illegitimacy. The police and courts enter the health field in alcoholism, sex offenses and insanity as well as crime. Through coroners, medical examiners and district attorneys, they deal with the medical problems of sudden or violent death. Every physician should know which deaths to report immediately to the medical examiner. The civil-defense department calls on physicians for medical planning and participation in preparation for disaster or enemy attack. These are samples only of the governmental health agencies at the municipal level with which all physicians sooner or later deal. It should be a part of the setting up of a practice by any medical practitioner to go to the offices of these agencies, learn what official procedures are required of physicians by the respective officials, and in what ways they can be of mutual service to each other. For the board of health not only demands reporting of contagious diseases but also often furnishes vaccines.

The police not only require reporting of certain offenses but also often supply oxygen, crutches and ambulance service in emergency. Not only does the town or city clerk insist on birth registrations; in many municipalities he pays for them. Usually the physician must register with him before opening an office. The physician needs to know when he can call on the district nurse, the social worker or the veterans-committee chairman. He must make himself acquainted with the procedures of the welfare department in obtaining municipal aid.

At the county level, it is wise to be familiar with the routines of district and superior court and grand jury. Some day the physician will be called on to testify. County tuberculosis sanatoriums are available in some states; these should be visited, and the requirements for admission studied. Such institutions often provide the best diagnostic technics in the region. If there is a county health officer or a health or diagnostic center these facilities should be studied.

The state department of health often furnishes complete diagnostic or bacteriologic laboratory service. It frequently supplies unusual vaccines or other immunization services or equipment. Whereas it requires venereal-disease reports, it also supplies serologic and bacteriologic tubes and culture mediums. The requirements for admission to state cancer and psychiatric hospitals should be learned. Many state laws demand specific duties of physicians, and a compendium of these should be acquired from the state capitol for ready reference. This is particularly true of regulations for the registration of physicians, which in some states must be renewed periodically. State agencies often supply special services for veterans, dependent children, the aged, the blind and the crippled. There are state-aided rehabilitation centers, mental-health clinics, industrial accident boards and clinics, schools for retarded children, clinics for alcoholism and employment services for the handicapped. Many of these services are obtainable through municipal application by the town or city welfare department or social worker, and this is usually the best source of information about them. But the local representative in the state legislature is often a good medium of inquiry if others fail; one should make his acquaintance in any case.

Federal agencies in the field of health are in a process of growth and transition so rapid that it is difficult to keep up with them. For this reason only the most general statements can be made about them. As they apply to the private practice of medicine, they group themselves chiefly about the United States Public Health Service, the Veterans Administration and the armed forces. Reference has already been made to immunization requirements of the State Department for foreign travel. The Public Health Service similarly affords vaccines for certain tropical diseases like yellow fever, usually through a governmental hospital in each geographic region. Its staff is available for special studies in widespread epidemics, and the practicing physician may need consultation or information from the Service in diagnostic or sanitation problems in this field. Many federal departments publish informational and educational pamphlets on such subjects as maternal and child health, industrial hazards and food and drug problems. The American Medical Association, through its Chicago offices, can often provide the best information on how to obtain from the Government materials and services in such special circumstances.

By far the greatest number of problems involving federal services arise in relation to the armed forces and the Veterans Administration. Members of the armed forces who are injured or taken sick while on leave are subject to special regulations that every physician sooner or later must know. In general an immediate report must be made to the commanding officer of the man involved, often through the local Red Cross chapter, and prompt transfer to a military hospital must usually be made unless special permission is obtained from the unit concerned. Military discipline and governmental responsibility are as serious factors in the situation as the disease, and the private physician really has no alternative, since the military patient is not in the position of a private contractor in hiring a physician. Physicians are therefore well advised to make themselves familiar at least with what military hospitals are available in the region, and how to communicate with them in cases of referral. Usually, these hospitals supply their own ambulance service. Often, they afford facilities for the hospitalization of the families of service men as well as of the men themselves. It is not good medical practice to charge expenses of private hospitalization to the family of an overseas soldier when a nearby Army hospital would have provided the same services free. Of course, exceptions to this principle exist among the well-to-do, but the principle holds in most cases.

The care of veterans is an even more difficult problem. At the time of writing the office care of veterans can be supervised by private-contract physicians who have obtained for themselves approval by the Veterans Administration. Monthly reports and renewals of authorization to continue the care of each veteran are required, and the regional Veterans Administration medical clinic usually sees the patient periodically for review of his need for further care. If the disability was incurred in the service the procedure remains relatively simple, but when other disabilities of nonservice-connected origin are involved, matters of ethics and of responsibility for the care of the patient sometimes make confusion worse confounded. The patient often becomes a segmented case, 30 per cent of him, representing the officially estimated disability, belonging to Veterans Administration care, and the other 70 per cent, not service

connected, belonging theoretically to the other medical resources of the community. Hospitalization in a Veterans Administration hospital almost inevitably occurs in nonservice-connected cases under these conditions, with or without real economic need for governmental subsidy of the patient. Only careful individual consideration of each case can justify fair decisions in these situations. The private physician has no formulas to follow, and must depend on individual judgment to guide him in advising the patient how to make proper use of the facilities offered by the Veterans administration. The physician needs to know his community veterans' committee, and should consult sometimes also with committees of the local veterans' organizations on special problems involving a patient. Local community agencies are often the only ones that can properly be used to study the needs of veterans with particularly difficult problems. Under present conditions there is no effective medical liaison between Veterans Administration hospitals and the family physician. Such a liaison often needs to be improvised with whatever means comes to hand at both hospital and community levels.

MEDICAL PROGRESS

TREATMENT OF BACTERIAL ENDOCARDITIS*

MAXWELL FINLAND, M.D.†

BOSTON

ONE of the great triumphs of this era of chemotherapy and antibiotics has been achieved in the treatment of bacterial endocarditis. This disease, which before the introduction of the sulfonamides was almost universally fatal, affords an undisputed demonstration of the life-saving properties of the antibacterial agents, penicillin standing out as by far the most impressive of the agents thus far available. Many articles in the medical literature attest to the limited value of sulfonamides and to the striking clinical effects and reduction in mortality attributable to penicillin in the treatment of large numbers of cases.

It is not the purpose of the present report to review the entire literature. Details and reviews on the use and results of the sulfonamides, with and without the addition of heparin and of induced fever, are given by Lichtman,[1] Kelson and White,[2] White, Mathews and Evans,[3] Kelson,[4] Smith, Sauls and Stone[5] and Schein and Baehr.[6] There are also a number of significant reports and reviews of the clinical and bacteriologic effects of penicillin[7-41]; some of them include details in patients who also received heparin or other anticoagulants.[7-10, 18, 19, 25, 28, 40, 41] Of particular interest are some of the early descriptions of treatment with penicillin in which the effects are described carefully and in considerable detail.[7-16, 18, 21, 23, 27, 31] A few reports have dealt especially with follow-up studies of patients treated with penicillin,[42-46] and there are also detailed descriptions and reviews of the anatomic changes in the heart and other organs in patients who died during or after treatment with this antibiotic, including some in whom the treatment had been quite successful.[47-53] One of the earliest and most comprehensive reviews of the use of penicillin in subacute bacterial endocarditis is that of Baehr and Gerber.[54] An analysis of the extensive British experience was made by Cates and Christie.[55] A comprehensive review of the status of the treatment of bacterial endocarditis was presented by Bloomfield[56] in the 1950 Conner Lecture of the American Heart Association, and he has more recently summarized the problems of diagnosis and prophylaxis.[57]

This paper presents a critical evaluation of certain aspects of the treatment of bacterial endocarditis that are of current interest. These include the present status of dosage and method of administration of penicillin; the status of the use of other antibiotics; the treatment of patients with negative blood cultures; the problem of prophylaxis; and miscellaneous features of interest.

DOSAGE AND METHOD OF ADMINISTRATION OF PENICILLIN

Because sufficient and accurate data are not available for a final definition of the optimum dosage forms and methods of administration of penicillin in cases of bacterial endocarditis, it may be of interest to discuss some aspects of this subject. Certain features of the dosage of penicillin, however, are now generally accepted[58-63] — namely, that large doses must be given continuously over long periods and that, although these doses may be roughly related to the results of tests for sensitivity of the infecting strain to penicillin in vitro,[59] it is often necessary to give much larger doses than the results indicate. Moreover, although large doses given for

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Aided by a grant from the United States Public Health Service.

†Associate professor of medicine, Harvard Medical School; chief, Fourth Medical Service, and associate director, Thorndike Memorial Laboratory, Boston City Hospital.

short periods have sometimes proved effective and have been suggested as a useful form of administration,[64] this method has also been tried and found wanting in many cases.[60]

It is generally agreed that in this disease oral administration is too unreliable and requires excessive amounts so that the use of penicillin in this form has generally been discarded as inadequate. Furthermore, in the dosages required, oral administration may have untoward gastrointestinal effects similar to those resulting from the oral use of the broad-spectrum antibiotics. Nevertheless, this form has undoubtedly been employed by many physicians in the management of patients who turned out to have bacterial endocarditis, particularly when they were treated at home, either entirely, or in the care after recovery, or subsequently, on occasions when prophylactic administration was required. Presumably, the oral route is at times successful, particularly when a very early infection with a highly susceptible organism is being treated with massive doses; it is more likely, however, that such usage is responsible for many therapeutic failures since it may serve as an excuse for the delay in instituting adequate treatment, particularly when there is temporary improvement. However, little of this type of experience is recorded, and therefore this assumption cannot be authenticated.

For some time, particularly during the first years after penicillin became freely and plentifully available, many workers considered the constant intravenous infusion and a few the constant intramuscular infusion of the soluble sodium salt to be the optimum method of treatment.[7, 9, 18, 21, 34, 65] Although the intravenous infusion is still preferred by some,[66] these methods have now for the most part been discarded as too cumbersome, too traumatic and of no particular advantage over the intermittent intramuscular method, which is now most widely preferred and employed.[36, 40, 54, 56, 67-69]

Repository forms of penicillin are probably the ones most frequently used for all purposes in the home and even in much hospital practice. These forms have the advantage of permitting fewer intramuscular injections, and with procaine penicillin such injections are probably less painful and thus more acceptable to the patient than the regular forms of sodium or potassium penicillin. It is for that reason that I should like to dwell on this phase.

There are reports of the successful use of most of the repository types of penicillin that have been widely available,[56, 70-75] including even penicillin in beeswax and oil,[70, 71] a form that, because of its irregular absorption and the frequent local reactions it produced,[71] has now been entirely abandoned in favor of procaine penicillin, either in aqueous suspension or in oil and aluminum monostearate.[72-74] The aqueous suspension is the form generally preferred[56, 72] and used in cases of bacterial endocarditis and in other infections requiring large doses and high concentrations of antibiotic. Administration of repository forms of penicillin has undoubtedly been successful and has been approved by some leading authorities[56] as probably adequate in cases due to highly sensitive organisms. However, in reviewing the records of previous therapy in many patients admitted to hospitals for treatment of subacute bacterial endocarditis one is impressed with the frequency with which these patients had been treated for long periods with various forms of procaine penicillin and yet were found to have bacteremia with highly sensitive organisms on admission. The use of the repository forms of penicillin has not usually been regarded as responsible for these failures.[73-75] Nevertheless, such experiences, when considered in the light of the nature of the lesion in subacute bacterial endocarditis on the one hand and the mechanism of action of penicillin and the manner in which it is absorbed and excreted in the body on the other, should lead to the conclusion that these repository forms do not provide optimum treatment in this disease. The nature of the lesion in bacterial endocarditis, particularly the importance of fibrin and connective tissue enclosing necrotic areas and dense masses of bacteria without access to blood vessels, has been adequately described[47-51] and has become quite familiar. However, some of the factors in the action of penicillin merit discussion, with particular reference to such lesions.

The extensive and carefully designed experiments of Eagle and his co-workers have helped to clarify in a large measure the mechanism by which penicillin, within certain limits, may continue to be effective in the interval between intermittent injections, at a time when the concentration at the site of infection falls below the minimum effective level.[76] They have also shown that the rate at which organisms are killed by penicillin varies with the particular organism and is determined in a large measure by the total time for which an effective concentration is provided at the site of infection.[77] However, the number of organisms is also highly important — the larger the number, the longer the need for effective treatment.[77] Their experiments, which employed an infectious focus that was adequately supplied with blood and tissue fluid, offered good opportunities for the diffusion of the antibiotic into the focus and thus provided access of penicillin to the organisms. Their experimental lesions also permitted access to leukocytes, and thus made possible the disposal of small numbers of organisms that might have escaped the bactericidal action of penicillin, and permitted a cure, in certain infections, through the mediation of immune mechanism of the host when the doses of penicillin were inadequate to sterilize the lesions completely.[78, 79]

In man, however, Eagle's experiments could not explain why high concentrations and long periods of treatment fail to cure some cases of subacute bacterial endocarditis in which the organism is not resistant in vitro.[77] He suggests that in this disease the focus of infection may be poorly supplied with nutrient or that the organisms may multiply so slowly that the drug is paradoxically inactive, since penicillin is effective primarily against actively multiplying organisms.[77] To these arguments may be added the factor of the population density of the organisms within the vegetations and the thick layer of fibrin and fibrous tissue that surrounds the bacteria.[80] Although these may not entirely prevent the access of penicillin they may delay and reduce the diffusion into the immediate vicinity of the organisms and also prevent access to antibodies and leukocytes. As a result there is little opportunity for the mediation of the host mechanism, even if high titers of antibodies against the infecting organisms are present in the serum.

Eagle and his associates[76, 81] calculated that from two to twenty times the minimum inhibitory concentration in vitro had to be provided in the serum to obtain the maximum effective level at the focus of infection with which they worked. When this reasoning is applied to the lesions in bacterial endocarditis, one must add the factor of poor diffusion into the focus, which depends on the amount of necrosis and walling off by fibrin and connective tissue, the poor blood supply and the heavy concentration of organisms — all of which indicate that even larger multiples of the minimum inhibiting concentrations in vitro would be required. This type of reasoning would help to explain why repository preparations of penicillin given at fairly long intervals have proved effective in the treatment of syphilis[81] when the organism is very sensitive, and against invasive lesions with highly sensitive organisms like Group A hemolytic streptococci but have often failed when more resistant organisms like *Streptococcus faecalis* are involved, or in staphylococcal infections when there are focal, necrotic and walled-off lesions.

Eagle and his co-workers[81] could find no evidence in their experimental model that penicillin remains at effective levels in tissues for significant periods after it has fallen below the serum concentrations. In this respect the experiments of Weinstein, Daikos and Perrin[82] are quite relevant. In attempting to simulate the conditions within the valvular lesions in subacute bacterial endocarditis these workers employed fibrin clots implanted subcutaneously in rabbits and then studied the diffusion into and out of the clot after intramuscular injections of penicillin. They found a direct relation between the size of the intramuscular dose and the duration and concentration of penicillin in the clots and presumably in the surrounding tissue menstruum. Using large doses, they observed that an equilibrium was established between the concentration of penicillin in the fibrin and in the surrounding menstruum within about two hours*; thereafter, penicillin could be demonstrated for longer periods and at higher concentrations within the clot than in the blood. Moreover, the larger the size of the individual dose, the longer penicillin could be demonstrated in the fibrin in higher concentrations than in the peripheral blood.

To return to the problem of absorption and excretion, one of the most striking features of the pharmacology of penicillin is the rapid rate at which it is cleared by the kidney. The renal clearance of this antibiotic in man approximates the total renal blood flow; it is about four or five times greater than the renal clearance of inulin and is independent of the absolute blood level over a wide range and is also independent of the rate of urine flow.[83] Since practically all the penicillin injected is eliminated in the urine, this fact has a direct bearing on the maximum blood level and on the duration for which high levels can be sustained in the blood and tissues. Thus, for any given amount that is injected, the more rapidly the penicillin reaches the blood, the higher the maximum blood level and the faster its fall. After an intravenous injection of any given amount the highest peak is reached very rapidly and is sustained only momentarily; the concentrations then drop very rapidly. When the same amount is given intramuscularly, the peak concentration is reached a little later and is sustained somewhat longer, and the concentrations fall at a slower rate, depending on how rapidly it diffuses out of the site of the intramuscular injection; in most patients and for most preparations and doses the fall in the levels is quite rapid. When repository preparations of penicillin are used, the more the absorption is delayed, the lower the maximum concentration that can be achieved, although that maximum concentration would be sustained for a longer time in the blood and correspondingly lower concentrations would be sustained over the longer periods.

From available evidence it seems reasonable to assume that the higher the concentration reached in the blood and the longer these high peaks are sustained, the better the diffusion into serous membranes and into walled-off foci of infection. Also, with the higher peak levels, the diffusion into serous cavities and infected foci should be better, and the effective concentrations be expected to stay longer at high levels within the tissue fluids, since the diffusion back out of these foci is also correspondingly slow. If the levels required at a focus of infection, such as that produced by Eagle et al.,[76] may be as much as five to twenty times the minimum inhibiting concentration in vitro it seems reasonable to assume that to get to the organ-

*This is usually an hour to an hour and a half after the peak concentration in the blood has been reached.

isms within a vegetation in subacute bacterial endocarditis, a considerably higher gradient must be needed. Moreover, because of the density of the bacterial population at this site, high concentrations must be required there, and the action must be more prolonged at these high levels.*

The validity of this explanation requires more definitive proof, but results in patients treated with antibiotics for subacute bacterial endocarditis and for other focal and well walled-off infections, such as those seen in well established staphylococcal infections, appear to be consistent with this type of mechanism. If this explanation is valid, repository preparations of penicillin should certainly not be recommended for use in bacterial endocarditis, or indeed in any infection characterized by walled-off lesions with central areas of necrosis, except possibly those due to the most susceptible types of organisms like the gonococcus, *Treponema pallidum*, or Group A hemolytic streptococcus.

In the treatment of subacute bacterial endocarditis such an explanation suggests the use of intermittent intramuscular injections of large individual doses of the soluble sodium or potassium salts of penicillin at intervals of two to four hours, as recommended by many workers[31, 56, 58, 68]; the largest doses and the shortest intervals would be reserved for infections with the most resistant organisms. The choice between the sodium or potassium salt should not be important except in patients with cardiac or renal failure. It is fair to assume, from the known pathology of the cardiac vegetations, that the conditions in infections of long standing provide a greater density of fibrin and connective-tissue layers and even some calcification in addition to the larger number of organisms that are found; such old lesions would therefore also call for an increase in the size of the dose and shortening of the interval between doses over those expected solely from the consideration of the sensitivity of the organism alone.

The same reasoning could be used to argue against the employment of the constant intravenous infusion, since peak levels are thus reduced as compared with those obtained from rapid injections of the same total amount of penicillin. However, it seems reasonable to employ intermittent and fairly rapid intravenous injections to achieve the highest attainable peaks, provided that a renal excretory inhibitor is also used for the purpose of reducing the rate at which the peak blood level declines; in this way it may be possible to prolong the duration of action within the focus. For this purpose the renal excretory inhibitor must be given in advance of the intravenous injections, and its administration continued throughout the period of such treatment. Such an agent, the most active one now available being probenecid (Benemid),[85] is likewise useful as an adjuvant in intermittent intramuscular treatment, particularly when one is dealing with organisms of moderate or high resistance or when the size of the individual doses required without the use of an adjuvant is so large as to be difficult for the patient to tolerate. The use of an excretory inhibitor also permits one to extend the length of the interval between intermittent injections and thus to reduce the number of injections given. Obviously, if there is already severe renal failure, as measured by retention of phenolsulfonephthalein, an adjuvant is not necessary since high levels may be sustained in such cases with considerably smaller doses than in persons with normal renal function.

So far as renal excretory inhibitors are concerned, intravenous administration of para-aminohippuric acid was first recommended and occasionally used,[86, 87] but this method was found to be too cumbersome. Caronamide by mouth has previously given quite satisfactory results,[88-92] but much larger doses of this agent are required as compared with probenecid and these doses sometimes produced untoward gastrointestinal symptoms. The dosage of probenecid that is generally effective is 0.5 gm. four times a day,[85, 93-95] but twice that amount may be required in some patients to obtain the optimum effect.

When probenecid is given in the treatment of bacterial endocarditis, since some patients have joint pains and may even have active rheumatic infection for which one may wish to prescribe a salicylate, it is important to bear in mind that, although this substance enhances the blood levels of para-aminosalicylic acid,[96] it does not do so for salicylates.[85] Moreover, although blood concentrations of penicillin and phenolsulfonephthalein are enhanced, the levels of chlortetracycline, oxytetracycline, chloramphenicol or streptomycin are not increased by the use of probenecid.[97]

Use of Other Antibiotics

There can be little doubt that, properly used, penicillin is the single agent responsible for the greatest majority of recoveries from bacterial endocarditis. This is to be expected from the fact that all but a comparatively small proportion of cases of subacute bacterial endocarditis and a significant proportion of those due to organisms besides *Str. viridans* are infections with organisms that are highly or moderately susceptible to penicillin.[39, 55, 68, 98-107] Furthermore, because of its relatively low toxicity, which permits massive doses, and because the levels attainable from such doses can be further enhanced by inhibition of the renal excretion through the use of such a drug as caronamide or probenecid, some cases due to organisms that are relatively resistant to penicillin have also been successfully treated with this agent alone.

*Eagle[68] considers prolonged treatment rather than more treatment more promising in a focus of infection with Group A hemolytic streptococci that are no longer multiplying within the focus; this opinion favors the use of repository penicillin preparations for such infections. Eagle also regards streptomycin as useful in bacterial endocarditis because it is active against organisms that are not multiplying.

Nevertheless, cases are being encountered, perhaps with increasing frequency,[80] in which penicillin alone, even when supplemented with adjuvants, fails to arrest the disease. In other cases the organisms are only slightly susceptible to different antibiotics when they are used alone, but there appears to be an additive or synergistic action of some of the other agents, particularly streptomycin[108-112] with penicillin in vitro, and their use may exert curative effects in cases of endocarditis only when properly combined with penicillin or possibly other antibiotics. In vitro observations, supported in some cases by experimental infections in animals, also suggest that for certain bacterial strains the action of some of the antibiotics may actually be antagonistic when used in certain combinations and may thus reduce the effectiveness of the individual agents.[108-116] It may, therefore, be of interest to discuss the treatment with antibiotics besides penicillin when those agents are used alone or in combinations, which may include penicillin. Many reports of cases treated with the newer antibiotics have appeared, most of them in the past three or four years. No attempt is made to review all these reports, but most of the readily accessible ones have been used as the basis for this presentation.

Streptomycin

When the use of streptomycin in subacute bacterial endocarditis was first reviewed by Hunter[117] he recorded the results in 18 cases, which included 6 of his own and 12 from records that had been collected by Keefer. Half the cases were infections with enterococci or with *Str. viridans;* 1 was due to *Staphylococcus aureus,* and the rest to gram-negative bacilli. Cures were reported in 4 cases and possibly in 4 others, and an additional patient achieved a remission for three months and failed to respond during a relapse. Hunter also referred to the earlier report of Priest and McGee,[118] who had treated 3 cases due to *Str. viridans* in which a favorable effect was achieved by streptomycin, but only 1 patient was actually cured by the use of this agent alone.

Since the appearance of Hunter's review, Keefer and Hewitt[119] have published the results of the extensive clinical trials of streptomycin carried out under the auspices of the National Research Council. This compilation includes the results of the use of streptomycin in 39 cases of bacterial endocarditis; most of these patients had also received penicillin and some had been given sulfonamides. In 17 patients the organism was a gram-negative bacillus; the disease was arrested in 6, and temporary improvement was obtained in 3 others. In addition there was a case of tularemia that was probably complicated by endocarditis and in which a rapid clinical cure was obtained, and another of brucella endocarditis in which temporary improvement resulted but an apparent cure was subsequently obtained only after treatment with sulfadiazine. The remaining 20 patients were treated for bacterial endocarditis due to gram-positive cocci; the infection was arrested in 6, and only temporary improvement was obtained in 5 additional ones. Thus, a third of the 39 patients were apparently cured by streptomycin, used in most cases in conjunction with penicillin, but in others it was apparently successful after the use of penicillin had failed.

In 1949 Wallach and Pomerantz[120] collected 50 cases of bacterial endocarditis in which the use of streptomycin had been reported before May of that year, and they added a case of endocarditis caused by bacteroides. Their review includes the cases previously reported by Hunter and possibly some additional cases that had been incorporated in Keefer and Hewitt's report. Nearly two thirds of the patients in this series had received penicillin before or during the treatment with streptomycin. These cases involved infections with 17 different organisms; of 33 due to gram-positive organisms, 18 were apparently favorably affected, and there were 19 due to gram-negative bacilli, of which 12 were successfully treated. Among the successful cases 2 were due to mixed infections (previously reported by Olinger[121]) and cured by penicillin and streptomycin; both were due to *Str. viridans,* mixed in 1 case with a diphtheroid and in the other with *Haemophilus parainfluenzae.* Thus, recovery followed treatment with streptomycin, with or without additional penicillin, in 28 of these 50 patients.

The major practical deduction that Wallach and Pomerantz[120] made from their review concerns the prognostic value of the results of in vitro tests for sensitivity of the organisms to streptomycin. Treatment was successful in 21 of 31 patients in whom the organism was sensitive to 9 microgm. per cubic centimeter or less, whereas only 1 patient was cured among 7 in whom more than 9 microgm. was required to inhibit the organism. However, there did not appear to be any correlation between the sensitivity of the strains and the dosage necessary to obtain a good result; dosages ranging from 0.5 to 6 gm. per day had been used, and 1 patient received up to 8 gm. per day.

It seems reasonable to assume that a sizable number of patients have been treated with streptomycin with or without penicillin since the appearance of the Wallach and Pomerantz review, and that probably only a small proportion of these cases have been recorded in the literature. Without any attempt to include all cases it was possible to collect reports of 76 additional cases not mentioned in the previous reviews.[28, 30, 36, 38, 91, 110, 111, 122-136] Only 6 of these cases[125-127, 134] were due to gram-negative bacilli, and there was only 1 failure[126] among the 6. There were 6 other patients in whom consistently negative blood cultures were obtained, and all recovered.[122, 130] The rest of the cases were due to gram-positive cocci, the largest proportion being enterococci. In

all but a few cases penicillin had also been used previously or simultaneously with the streptomycin. Treatment was successful in 57 of the entire group of 76 patients.

In this series, as in that of Wallach and Pomerantz,[120] there was a good correlation between the sensitivity of the infecting organism to streptomycin and the results of treatment. Of 17 patients in whom the organism was sensitive to 10 microgm. per cubic centimeter or less, 16 were cured and there was only 1 failure, whereas among 15 cases in which inhibition of the organisms required 12.5 microgm. or more, there were only 5 cures, failures occurring in 10 cases.

If these results are to be considered at their face value, there appears to have been a definite and steady improvement in the recovery rates in patients treated with streptomycin — from 33 per cent in the collected series of Keefer and Hewitt to 56 per cent in the cases collected by Wallach and Pomerantz, and finally 75 per cent recoveries in the last group of cases, almost all of which were reported after those included in the previous summaries. This apparent increase in effectiveness of therapy may have been due in some measure to the inclusion of larger proportions of favorable cases; this would be consistent with the smaller proportion of cases of infection with gram-negative bacilli in these successive reports. It is equally possible, and perhaps more likely, that the improved results in the more recent cases were due, in large part at least, to the use of larger doses of penicillin in conjunction with the streptomycin for the treatment of infections with gram-positive organisms that are only moderately sensitive to penicillin and on which streptomycin exerts a moderate or marked inhibitory effect, either alone or in conjunction with penicillin.

The problem of the development of resistance during treatment is always one of the most important considerations in the use of streptomycin. This may occur with extreme rapidity in certain types of infections, notably in those of the urinary tract,[137] and is readily and rapidly demonstrated during exposure of many types of organisms to streptomycin in vitro.[138] It is therefore surprising that this phenomenon has not been reported more often in cases of bacterial endocarditis treated with this antibiotic. The development of an increase in resistance to streptomycin during the course of treatment with this antibiotic alone, however, has been recorded in at least 4 cases,[117, 132, 134, 139] but only in 1 was there a great increase in resistance in an organism (*Gaffkya tetragena*) that had been quite sensitive before the start of streptomycin administration.[132] From personal observations, I have the distinct impression that the development of resistance to streptomycin is being encountered more frequently than one would be led to suppose from the published reports, but this occurs primarily during periods when streptomycin is being given alone. It has occurred, however, when streptomycin was given in combination with another antibiotic but only when the organism was already resistant to the second agent at the time when the treatment with the combination was started.

In vitro experiments carried out in the Thorndike Memorial Laboratory have indicated that when staphylococci are repeatedly subcultured in increasing concentrations of a combination of penicillin and streptomycin, resistance to these agents, although not entirely prevented, may be delayed and depressed as compared to that which develops when the same organisms are exposed to increasing concentrations of the individual antibiotics of the combination. This was also found to be true for some strains of *Str. viridans* and enterococcus, although these organisms did not usually become resistant to the antibiotics, especially to penicillin, as readily as the staphylococci.[140] Moreover, it was necessary that the organisms be originally sensitive to both antibiotics for the delay or suppression of resistance to be demonstrable during simultaneous exposure to the pair of agents.[141]

Other in vitro studies[108-111, 116] have indicated that antagonistic action between penicillin and streptomycin does not occur but that usually these agents act in an additive, and sometimes in a potentiating or synergistic manner, if the latter term is used to denote more than an additive effect.

From these observations, it appears that streptomycin may be a useful antibiotic, both when used alone for the treatment of infections with organisms that are highly sensitive to it and when given in combination with large doses of penicillin for the treatment of bacterial endocarditis due to organisms that are moderately sensitive to each of these agents or highly sensitive to one of them. In cases in which the organisms are sensitive or only moderately sensitive to both agents the combination may be effective not only by their additive or possibly synergistic action but also by delaying or preventing the development of resistance in the organisms to either or both of these agents. The latter effect has not been conclusively demonstrated in vivo, but if it proves to be true, it would permit continuous antibiotic activity over a longer period when the decrease in the number of organisms in the lesion is proceeding at a slow rate.

Since streptomycin must be given continuously and over fairly long periods in the treatment of cases of bacterial endocarditis, its toxicity may be of some consequence — eighth-nerve damage[30, 36, 124, 127, 130] and hypersensitivity reactions[91, 134] have occurred. Although many of the recent reports of cases of bacterial endocarditis have followed the general trend of substituting dihydrostreptomycin for streptomycin, there does not seem to be any sound basis for such usage.[142] Both cause damage to the eighth nerve when they are used in

moderate or large doses continuously over long periods; with dihydrostreptomycin, loss of hearing may be more common and may occur in about the same frequency as the vestibular damage from the use of streptomycin.[143] Sensitization reactions, however, are somewhat less frequent with dihydrostreptomycin; when sensitization occurs with the administration of streptomycin, a change to dihydrostreptomycin can generally be made without further reaction, at least for some time.

There is some recent evidence that the eighth-nerve toxicity from both agents may be greatly reduced and possibly eliminated by the use of the two forms in a 1:1 ratio.[144] However, until this is demonstrated in a large number of cases, it appears safer to use one and then change to the other at the first evidence of toxicity. Deafness after dihydrostreptomycin is often insidious in its appearance and may not be made out until after treatment has been stopped; it may therefore be better to start with streptomycin, particularly since vestibular changes are more readily detected clinically and may be more transient. It may then be possible to return to the use of streptomycin after a period of treatment with dihydrostreptomycin to complete the long course of therapy that is usually required.

Bacitracin

This antibiotic is active primarily against gram-positive organisms.[145] It has been placed by Jawetz, together with penicillin and streptomycin, among the Group 1 antibiotics[116]; agents in this group, from available experimental evidence, may exert additive or synergistic effects on one another, but have not been shown to exert antagonistic action in vitro. The action of agents of Group 1 on highly sensitive organisms is sometimes antagonized by antibiotics of Group 2, which includes the broad-spectrum antibiotics. However, against organisms resistant or only moderately sensitive to the antibiotics of Group 1, the Group 2 agents may be additive or potentiating. Bachman[146] has presented data showing the synergistic action of penicillin and bacitracin in vitro against some but not all strains of alpha-hemolytic and nonhemolytic streptococci that he tested.

The results of the use of bacitracin have thus far been reported in very few patients with bacterial endocarditis,[147-154] but these results have been highly favorable. Most of the detailed reports pertain to single cases, and only one concerns 3 patients.[148] Among a total of 10 such recorded cases in which details are given, 9 patients responded favorably and were cured. In these 9 patients the infections were due to a staphylococcus and an enterococcus, each in 1 case, to a diphtheroid bacillus in 2 cases and to various nonhemolytic streptococci in the remaining 5. In all but 1[152] of these cases penicillin was also used, and in 3[150, 154] other antibiotics had been given in addition. The patient in whom bacitracin alone was successful[152] had an endocarditis due to a diphtheroid bacillus that had previously failed to respond favorably to penicillin given alone and in combination with streptomycin. The only recorded failure[153] was in a case of pneumococcal endocarditis in which treatment with bacitracin alone was begun for pneumonia with bacteremia due to pneumococcus Type 2. The patient had a murmur at the time of admission to the hospital, and endocarditis apparently developed under treatment with increasing doses of bacitracin, up to nearly 400,000 units a day. In most of the other patients the daily dose was 100,000 units or less given in three or four intramuscular injections. In an additional patient,[136] not included in the preceding discussion, bacitracin was given for a short time for the treatment of an enterococcal endocarditis and stopped as soon as casts were noted in the urine, so that its effect on the disease could not be determined.*

In addition to these detailed reports Smith, in a personal communication to Welch and Lewis,[145] reported on the use of penicillin and bacitracin, in a ratio of 10:1 units, in the treatment of 30 patients with subacute bacterial endocarditis. Most of these patients received 1,000,000 units of penicillin and 100,000 units of bacitracin daily, and the results were considered excellent. No further details are given beyond the statement that at this dosage level, little or no nephrotoxicity was observed.

From these inadequate data it appears that bacitracin, used in doses of 100,000 units daily in three or four doses together with large doses of penicillin, may provide a highly useful method of treating patients with endocarditis due to gram-positive organisms that are only slightly or moderately sensitive to penicillin. The use of bacitracin in bacterial endocarditis, as in many other medical diseases, however, has been limited chiefly because of the nephrotoxicity of this agent. On parenteral administration, especially when large doses are used, there may be moderate to marked reduction in renal plasma flow, and in glomerular filtration, and these are associated with albuminuria, microscopical hematuria and the appearance of epithelial cells and granular casts.[153, 157] In moderate doses (100,000 units per day or less) evidence of moderate and transient renal toxicity appears in 30 per cent of the cases and is only rarely disturbing; the changes in renal function and in the urinary findings are usually reversible soon after the drug is stopped.[158]

Meleney et al.[158] have tended to minimize the importance of the nephrotoxicity of bacitracin, emphasizing the need for rigid criteria on the part of manufacturers in the selection of lots of this antibiotic before they are released for parenteral

*An additional case in which the patient died is listed, without details, among the cases treated with bacitracin by Longacre and Waters.[155] Meleney and Johnson[156] also mention 8 cases of endocarditis treated with bacitracin systemically without benefit.

injection. Others[159, 160] have not shared his view; according to one group of workers[160] the nephrotoxicity of commercial preparations of bacitracin is due, in part at least, to the antibacterially active constituents, and there appears to be little hope of obtaining a preparation of bacitracin that does not have the capacity to damage the kidneys.[160] In view of the fact that renal lesions are already present in a large proportion of cases of subacute bacterial endocarditis at the time when treatment is undertaken, there is particular reason to be cautious and especially to avoid excessive doses in the treatment of this disease.

From the meager data thus far available, it appears that doses of about 100,000 units of bacitracin a day given in three or four injections may be safely used in this disease and apparently would produce only minimal renal damage, which should not be disturbing and which should be readily reversible. Bacitracin may therefore be used in this manner, in conjunction with moderate to large doses of penicillin, for the treatment of endocarditis due to organisms that are only moderately sensitive or relatively resistant to penicillin. Nevertheless, until further detailed reports of larger numbers of patients treated with this agent become available, its exact place in the treatment of endocarditis cannot be determined.

Broad-Spectrum Antibiotics

It is difficult to assess the true value of the so-called broad-spectrum antibiotics — namely, chlortetracycline, oxytetracycline and chloramphenicol — in the treatment of the bacterial endocarditides. This is due, in part at least, to the fact that in most patients the infecting organism is at least moderately sensitive to penicillin, alone or in conjunction with streptomycin, and some patients have already received treatment with one or both of these agents, perhaps with inadequate doses or not quite long enough to effect a complete cure; also, in a number of cases one or both of these antibiotics have actually been used in conjunction with the broad-spectrum antibiotics. However, a brief résumé of the results in a number of cases collected at random from the accessible literature may be of interest.

Chlortetracycline. Published reports on a total of 67 patients with bacterial endocarditis treated with chlortetracycline were collected.[75, 94, 95, 103, 110, 111, 150, 154, 161-174] Most of these patients received all the drug orally; some received it by intravenous injection, either at the beginning of treatment or intermittently during the course of oral therapy, or at both times, and at least 1 patient, who was successfully treated, received daily intravenous injections for twenty-six days.[170] The dosages ranged from 2 to 6 gm. a day by mouth, and usually 1 gm. a day in two doses intravenously. Gastrointestinal symptoms were frequent with oral therapy, but these were generally mild and temporary and, except in 2 or 3 patients, did not interfere with continuous therapy.

The treatment was successful, in that clinical and bacteriologic cures were obtained in 24 of these patients, but in some of them the role of the antibiotic in the recovery is not entirely clear.[162, 170] A few of these patients had previously failed to respond to treatment with penicillin with or without streptomycin.[103, 150, 167, 170, 174] On the other hand, other antibiotics were given together with the chlortetracycline in 8 of these cured patients,[103, 133, 150, 167, 169, 170, 174] penicillin in 4, penicillin with streptomycin in 2 and with bacitracin in 1, and oxytetracycline in 1. The causative organisms in the successfully treated cases were *Str. viridans* in 9, an enterococcus in 5, *Staph. aureus* in 6 and *Staph. albus* in 2, whereas in 2 patients all blood cultures were negative.[171]

Chlortetracycline failed to cure 43 patients. The following organisms were involved in these failures: *Str. viridans* (alpha or gamma) in 12 (2 of these were microaerophilic[162]), enterococcus in 17 (one was later mixed with *Aerobacter aerogenes*[169]), beta-hemolytic streptococcus in 1, *Staph. aureus* in 5, a pneumococcus in 3 and *Escherichia coli* in 1. In the 4 remaining patients, all blood cultures yielded no growth. There was 1 patient with pneumococcal meningitis and endocarditis in whom a bacteriologic cure was obtained and death resulted from a ruptured cusp of the aortic valve,[167] and another with pneumococcal endocarditis who died rapidly of cardiac failure after blood cultures had become negative.[167]

Most of these unsuccessfully treated patients received the antibiotic alone for part or all of the unsuccessful course of treatment, and only a few were given penicillin together with the chlortetracycline. There were 18 patients, however, in whom a cure was subsequently obtained by other treatment: 12 with large doses of penicillin, either alone or together with streptomycin,[94, 95, 103, 110, 111, 161, 167, 171] 1 with these two agents and bacitracin,[171] and 1 each with chloramphenicol,[169] chloramphenicol in addition to penicillin,[75] oxytetracycline and cortisone,[172] all 5 available antibiotics (including chlortetracycline) and a sulfonamide[171] and possibly cortisone alone.[172] In those subsequently cured the infecting organism was *Str. viridans* in 8, an enterococcus in 5, a pneumococcus in 1 and *Staph. aureus* in 1; the other 3 had negative blood cultures throughout.

In a large proportion of the cases in which no bacteriologic cure was obtained clinical improvement and negative blood cultures were observed for varying intervals and in some cases for long periods while the chlortetracycline was being administered, but a relapse of fever and symptoms with return of bacteremia followed a few days after administration was discontinued. As far as could be determined, failure was associated with a significant increase in resistance of the offending organism in only 1 case,

in which the inhibiting concentration of a staphylococcus increased from 5 to 40 microgm. per cubic centimeter in three days.[108] There were, among the failures, 4 additional cases in which the values recorded for sensitivity increased during treatment more than fourfold to values ranging from 2.0 to 6.2 microgm. from concentrations below 0.8 microgm. per cubic centimeter[162, 164, 171] and a fifth in which an apparent increase in resistance from 0.09 to 25 microgm. per cubic centimeter occurred during therapy with penicillin alone (this patient had received chlortetracycline before the first of these organisms was obtained[75]).

Apart from these findings, the sensitivities of the infecting organisms, among those tested, appeared quite similar in the cured patients to those in whom this antibiotic failed. Thus, among 14 strains obtained from cured patients before chlortetracycline was started, 11 were inhibited by concentrations of 1.0 microgm. per cubic centimeter or less, and 3 required more than 1.0 microgm.; among the cases in which no cure was obtained 19 strains were inhibited by 1.0 microgm. per cubic centimeter or less, and 6 required more than that concentration to inhibit the causative organism. In 1 of the cured cases the organism apparently increased in resistance from 0.3 to 2.5 microgm. per cubic centimeter during treatment with chlortetracycline alone, but the patient was subsequently cured by treatment with the combination of penicillin and chlortetracycline.[167]

If these results are considered at their face value, chlortetracycline appeared to be effective in less than half the cases of infections with *Str. viridans* (9 cures in 21 cases) and in more than half the staphylococcal infections (8 cures among 14 cases), but in only a small proportion of the cases of enterococcal endocarditis, only 5 cures having been achieved in 22 such cases. The value of the drug in the cases of pneumococcal endocarditis was difficult to assess because of the rapidly fatal cardiac lesions, but the bacteriologic results were favorable in 2 of the 3 cases.[167] It may have been responsible for the cure in 2 of the 6 cases with negative blood cultures, but in such cases the value of the therapy is difficult to assess.

Many observers have attributed failures to the fact that chlortetracycline is bacteriostatic and not bactericidal for the offending organism in the concentrations that could be attained at the site of infection.[109] This explanation appears to be reasonable from in vitro studies, and also from observations in a number of patients in whom clinical and bacteriologic remission and persistently negative blood cultures were obtained throughout long periods of treatment, to be followed by prompt clinical and bacteriologic relapses after discontinuance of administration. However, this may be an oversimplification, since similar treatment in comparable cases appears to be effective in some cases and fails in others. Other factors probably contribute to the failures, including the failure of adequate concentrations to reach the infectious site, poor absorption and increased destruction in the body. It must be admitted that the exact reason why this antibiotic acts favorably in the cure of this and many other infections and fails in some infections with organisms that are highly sensitive in vitro is poorly understood.

(To be concluded)

References

1. Lichtman, S. S. Treatment of subacute bacterial endocarditis: current results. *Ann. Int. Med.* **19**:787-794, 1943.
2. Kelson, S. R., and White, P. D. Notes on 250 cases of subacute bacterial (streptococcal) endocarditis studied and treated between 1927 and 1939. *Ann. Int. Med.* **22**:40-60, 1945.
3. White, P. D., Mathews, M. W., and Evans, E. Notes on treatment of subacute bacterial endocarditis encountered in 88 cases at Massachusetts General Hospital during six year period 1939 to 1944 (inclusive). *Ann. Int. Med.* **22**:61-74, 1945.
4. Kelson, S. R. Observations on treatment of subacute bacterial (streptococcal) endocarditis since 1939. *Ann. Int. Med.* **22**:75-96, 1945.
5. Smith, C., Sauls, H. C., and Stone, C. F. Subacute bacterial endocarditis due to Streptococcus viridans: survey of present status of previously reported cures and clinical study of fifteen treated cases, including another cure. *J. A. M. A.* **119**:478-482, 1942.
6. Schein, J., and Baehr, G. Sulfonamide therapy of subacute bacterial endocarditis. *Am. J. Med.* **4**:66-72, 1948.
7. Loewe, L. Combined use of anti-infectives and anticoagulants in treatment of subacute bacterial endocarditis. *Bull. New York Acad. Med.* **21**:59-86, 1945.
8. Dawson, M. H., and Hunter, T. H. Treatment of subacute bacterial endocarditis with penicillin: results in 20 cases. *J. A. M. A.* **127**: 129-137, 1945.
9. *Idem.* Treatment of subacute bacterial endocarditis with penicillin: second report. *Ann. Int. Med.* **24**: 170-185, 1946.
10. Meads, M., Harris, H. W., and Finland, M. Treatment of bacterial endocarditis with penicillin: experiences at Boston City Hospital during 1944. *New Eng. J. Med.* **232**:464-474, 1945.
11. Bloomfield, A. L., Armstrong, C. D., and Kirby, W. M. M. Treatment of subacute bacterial endocarditis with penicillin. *J. Clin. Investigation* **24**:251-267, 1945.
12. Bloomfield, A. L., and Halpern, R. M. Penicillin treatment of subacute bacterial endocarditis: some problems. *J. A. M. A.* **129**: 1135-1141, 1945.
13. Dolphin, A., and Cruickshank, R. Penicillin therapy in acute bacterial endocarditis. *Brit. M. J.* **1**:897-901, 1945.
14. Anderson, D. G., and Keefer, C. S. Treatment of nonhemolytic streptococcus subacute bacterial endocarditis with penicillin. *M. Clin. North America* **29**:1129-1153, 1945.
15. Favour, C. B., Janeway, C. A., Gibson, J. G., III, and Levine, S. A. Progress in treatment of subacute bacterial endocarditis. *New Eng. J. Med.* **234**:71-77, 1946.
16. Glaser, R. J., Smith, R. O., Harford, C. G., and Wood, W. B., Jr. Treatment of bacterial endocarditis with penicillin. *J. Lab. & Clin. Med.* **31**:291-312, 1946.
17. Ward, G. E. S., Meanock, R. I., Selbie, F. R., and Simon, R. D. Treatment of subacute bacterial endocarditis by penicillin: preliminary report on 18 cases. *Brit. M. J.* **1**:383-386, 1946.
18. Mokotoff, R., Brams, W., Katz, L. N., and Howell, K. M. Treatment of bacterial endocarditis with penicillin: results of 17 consecutive cases. *Am. J. M. Sc.* **211**:395-416, 1946.
19. Levy, L., and McKrill, N. Results in treatment of subacute bacterial endocarditis. *Arch. Int. Med.* **77**:367-384, 1946.
20. Lyon, R. A. Use of penicillin in treatment of subacute bacterial endocarditis in children. *J. Pediat.* **29**:560-566, 1946.
21. Geiger, A. J. Penicillin therapy in subacute bacterial endocarditis. *Mississippi Valley M. J.* **69**:2-16, 1947.
22. Seabury, J. H. Subacute bacterial endocarditis: experiences during past decade. *Arch. Int. Med.* **79**:1-21, 1947.
23. Jones, A. M., Herring, R., Langley, F. A., and Oleesky, S. Penicillin treatment of subacute bacterial endocarditis. *Brit. Heart J.* **9**: 38-64, 1947.
24. Wilhelm, F., Hirsh, H. L., Hussey, H. H., and Dowling, H. F. Treatment of acute bacterial endocarditis with penicillin. *Ann. Int. Med.* **26**:221-230, 1947.
25. Thill, C. J., and Meyer, O. O. Experiences with penicillin and dicumarol in treatment of subacute bacterial endocarditis. *Am. J. M. Sc.* **213**:300-307, 1947.
26. Priest, W. S., Smith, J. M., and McGee, C. J. Penicillin therapy of subacute bacterial endocarditis: study of end results in thirty-four cases, with particular reference to dosage, methods of administration, criteria for judging adequacy of treatment and probable reasons for failures. *Arch. Int. Med.* **79**:333-359, 1947.
27. Paul, O., Bland, E. F., and White, P. D. Bacterial endocarditis: experiences with penicillin therapy at Massachusetts General Hospital, 1944-1946. *New Eng. J. Med.* **237**:349-354, 1947.

28. Sirota, J. H., Gerber, I. E., and Baehr, G. Chemotherapy of subacute enterococcus endocarditis. *J. Mt. Sinai Hosp.* **14**:604-617, 1947.

29. Scheifley, C. H., and Hagedorn, A. B. Treatment of subacute bacterial endocarditis: report of forty cases. *Proc. Staff Meet., Mayo Clin.* **22**:527-530, 1947.

30. Zeller, W. W., Hirsh, H. L., Dowling, H. F., Hussey, H. H., and Robinson, J. A. Treatment of bacterial endocarditis with penicillin and streptomycin. *M. Ann. District of Columbia* **17**:21-31, 1948.

31. Tumulty, P. A., and Harvey, A. McG. Experiences in management of subacute bacterial endocarditis treated with penicillin. *Am. J. Med.* **4**:37-54, 1948.

32. Pearsall, H. R., Pillow, R. P., and Wood, J. E., Jr. Observations on treatment of subacute bacterial endocarditis with penicillin and streptomycin. *Am. Pract.* **2**:497-506, 1948.

33. Keefer, C. S., Anderson, D. G., and Hewitt, W. L. End results in treatment of bacterial endocarditis. *Tr. A. Am. Physicians* **61**:112-117, 1948.

34. Flippin, H. F., Mayock, R. L., Murphy, F. D., and Wolferth, C. C. Penicillin in treatment of subacute bacterial endocarditis; preliminary report on twenty cases treated over one year ago. *J. A. M. A.* **129**:841-843, 1945.

35. Matthew, H., and Gilchrist, A. R. Subacute bacterial endocarditis and its treatment with penicillin. *Edinburgh M. J.* **56**:25-48, 1949.

36. Drake, E. H., and Denham, R. M. Therapy of subacute bacterial endocarditis: report of 24 cases treated with penicillin. *Am. J. M. Sc.* **217**:485-493, 1949.

37. Williams, R. K., and Nelson, K. Treatment of bacterial endocarditis: review of 12 cases. *Virginia M. Monthly* **76**:589-593, 1949.

38. Griffith, G. C., and Levinson, D. C. Subacute bacterial endocarditis: report on 57 patients treated with massive doses of penicillin. *California Med.* **71**:403-408, 1949.

39. Loewe, L. Subacute bacterial endocarditis: diagnosis and present day treatment. *Am. Pract.* **1**:349-361, 1950.

40. Orgain, E. S., and Donegan, C. K. Treatment of bacterial endocarditis. *Ann. Int. Med.* **32**:1099-1113, 1950.

41. Cohen, S. M. Massive cerebral hemorrhage following heparin therapy in subacute bacterial endocarditis: report of two cases with review of literature. *J. Mt. Sinai Hosp.* **16**:214-230, 1949.

42. Loewe, L., Rosenblatt, P., and Greene, H. J. Combined penicillin and heparin therapy of subacute bacterial endocarditis: progress report of first seven consecutive successfully treated patients. *Bull. New York Acad. Sc.* **22**:270-272, 1946.

43. Kaplan, S. R., Rosenman, R. H., Katz, L. N., and Brams, W. A. Healed subacute bacterial endocarditis: new entity. *J. A. M. A.* **141**:114-116, 1949.

44. Hantschmann, L., and Trube, H. J. Zur Penicillinbehandlung der Endocarditis lenta. *Med. Klin.* **45**:428-432, 1950.

45. Pillsbury, P. L., and Fiese, M. J. Subacute bacterial endocarditis: follow-up study of thirty patients treated with penicillin. *Arch. Int. Med.* **85**:675-690, 1950.

46. Gorlin, R., Favour, C. B., and Emery, F. J. Long-term follow-up study of penicillin-treated subacute bacterial endocarditis. *New Eng. J. Med.* **242**:995-1001, 1950.

47. Carnes, W. H., and Tinsley, C. M. Pathological results in cases of bacterial endocarditis treated with penicillin. *Stanford M. Bull.* **4**:78-89, 1946.

48. Geiger, A. J., and Durlacher, S. H. Fate of endocardial vegetations following penicillin treatment of bacterial endocarditis. *Am. J. Path.* **23**:1023-1035, 1947.

49. Priest, W. S., Smith, J. M., and McGee, C. J. Effect of anticoagulants on penicillin therapy and pathologic lesion of subacute bacterial endocarditis. *New Eng. J. Med.* **235**:699-706, 1946.

50. Moore, R. A. Cellular mechanism of recovery after treatment with penicillin. I. Subacute bacterial endocarditis. *J. Lab. & Clin. Med.* **31**:1279-1293, 1946.

51. Correll, H. L., Lubitz, J. M., and Lindert, M. C. F. Bacterial endocarditis: clinico-pathologic studies of untreated and cured patients. *Ann. Int. Med.* **35**:45-58, 1951.

52. Perry, E. L., Fleming, R. G., and Edwards, J. E. Myocardial lesions in subacute bacterial endocarditis. *Ann. Int. Med.* **36**:126-137, 1952.

53. Spain, D. M., and King, D. W. Effect of penicillin on renal lesions of subacute bacterial endocarditis. *Ann. Int. Med.* **36**:1086-1089, 1952.

54. Baehr, G., and Gerber, D. E. Penicillin treatment of subacute bacterial endocarditis. *Adv. Int. Med.* **2**:308-349, 1947.

55. Cates, J. E., and Christie, R. V. Subacute bacterial endocarditis: review of 442 patients treated in 14 centres appointed by Penicillin Trials Committee of Medical Research Council. *Quart. J. Med.* **20** N. S.: 93-130, 1951.

56. Bloomfield, A. L. Present status of treatment of subacute bacterial endocarditis. *Circulation* **2**:801-810, 1950.

57. *Idem.* Diagnosis and prevention of bacterial endocarditis. *Circulation* **8**:290-296, 1953.

58. Hirsh, H. L., and Dowling, H. F. Treatment of Streptococcus viridans endocarditis with penicillin. *South. M. J.* **39**:55-60, 1946.

59. Bloomfield, A. L. Relation of strain sensitivity to curative dose of penicillin in subacute bacterial endocarditis. *Acta med. Scandinav.* Supp. **196**:505-515, 1947.

60. King, F. H., Schneierson, S. S., Sussman, M. L., Janowitz, H. D., and Stollerman, G. H. Prolonged moderate dose therapy versus intensive short term therapy with penicillin and caronamide in subacute bacterial endocarditis. *J. Mt. Sinai Hosp.* **16**:35-46, 1949.

61. Christie, R. V. Penicillin in subacute bacterial endocarditis. *Brit. M. J.* **2**:950, 1949.

62. Kleinfelder, H. Zur Klinik und Therapie der Endokarditis lenta unter besonderer Berücksichtigung der Behandlung mit Streptomycin und hohen Penicillindosen. *Ztschr. klin. Med.* **148**:53-59, 1951.

63. Keefer, C. S. Present day treatment of subacute bacterial endocarditis. *J. A. M. A.* **152**:1397-1400, 1953.

64. Hamburger, M., and Stein, L. Streptococcus viridans subacute bacterial endocarditis: two week treatment schedule with penicillin. *J. A. M. A.* **149**:542-545, 1952.

65. Goerner, J. R., Geiger, A. J., and Blake, F. G. Treatment of subacute bacterial endocarditis with penicillin: report of cases treated without anticoagulant agents. *Ann. Int. Med.* **23**:491-519, 1945.

66. Herrell, W. E. Antibiotic and chemotherapeutic agents in infections of blood stream and heart. *J. A. M. A.* **150**:1450-1455, 1952.

67. Christie, R. V. Penicillin in subacute bacterial endocarditis: report to Medical Research Council on 147 patients treated in 14 centres appointed by Penicillin Clinical Trials Committee. *Brit. M. J.* **1**:381-383, 1946.

68. Gerber, I. E., Shwartzman, G., and Baehr, G. Penetration of penicillin into foci of infection. *J. A. M. A.* **130**:761-764, 1946.

69. Snyderman, R., and Tipping, J. S. Subacute bacterial endocarditis. *Am. J. Med.* **6**:336-340, 1949.

70. Geiger, A. J., and Goerner, J. R. Treatment of subacute bacterial endocarditis with penicillin in peanut oil and beeswax. *New Eng. J. Med.* **235**:285-288, 1946.

71. Kennedy, B. J., and Seed, J. Treatment of subacute bacterial endocarditis with penicillin in beeswax-peanut oil; gluteal abscesses and rupture of spleen. *Am. Heart J.* **34**:906-912, 1947.

72. Roston, E. H., and Stollerman, G. H. Procaine penicillin in treatment of subacute bacterial endocarditis. *Am. Pract.* **4**:102-106, 1949.

73. Chertack, M. M., Best, W. R., and Hick, F. K. Treatment of subacute bacterial endocarditis with massive doses of procaine penicillin in oil. *Illinois M. J.* **100**:228-231, 1951.

74. Bader, M., Bader, R., and Friedberg, C. K. Causes of failure in treatment of subacute bacterial endocarditis. *J. A. M. A.* **148**: 1498-1501, 1952.

75. Ahern, J. J., and Kirby, W. M. M. Cure of subacute bacterial endocarditis with penicillin and chloramphenicol. *J. A. M. A.* **150**: 33-35, 1952.

76. Eagle, H., Fleischman, R., and Levy, M. "Continuous" vs. "discontinuous" therapy with penicillin: effect of interval between injections on therapeutic efficacy. *New Eng. J. Med.* **248**:481-488, 1953.

77. Eagle, H., Fleischman, R., and Musselman, A. D. Effect of schedule of administration on therapeutic efficacy of penicillin: importance of aggregate time penicillin remains at effectively bactericidal levels. *Am. J. Med.* **9**:280-299, 1950.

78. *Idem.* Bactericidal action of penicillin in vivo: participation of host, and slow recovery of surviving organisms. *Ann. Int. Med.* **33**: 544-571, 1950.

79. Eagle, H., Fleischman, R., and Levy, M. Effect of prior immunization on bactericidal action of penicillin in vivo. *Proc. Soc. Exper. Biol. & Med.* **82**:201-205, 1953.

80. Hunter, T. H. Treatment of some bacterial infections of heart and pericardium. *Bull. New York Acad. Med.* **28**:213-228, 1952.

81. Eagle, H., Fleischman, R., and Musselman, A. D. Effective concentrations of penicillin in vitro and in vivo for streptococci, pneumococci and Treponema pallidum. *J. Bact.* **59**:625-643, 1950.

82. Weinstein, L., Daikos, G. K., and Perrin, T. S. Studies on relationship of fluid and blood levels of penicillin. *J. Lab. & Clin. Med.* **38**:712-718, 1951.

83. Eagle, H., and Newman, E. Renal clearance of penicillins F, G, K and X in rabbits and man. *J. Clin. Investigation* **26**:903-918, 1947.

84. Eagle, H. Experimental approach to problem of treatment failure with penicillin. I. Group A streptococcal infection in mice. *Am. J. Med.* **13**:389-399, 1952.

85. Council on Pharmacy and Chemistry. New and non-official remedies — Probenecid. *J. A. M. A.* **151**:298, 1953.

86. Loewe, L., Rosenblatt, P., and Alture-Werber, E. Refractory case of subacute bacterial endocarditis due to *Veillonella gazogenes* clinically arrested by combination of penicillin, sodium para-aminohippurate and heparin. *Am. Heart J.* **32**:327-338, 1946.

87. Wall, R., and Brundage, O. Treatment of subacute bacterial endocarditis with penicillin and sodium para-aminohippurate by continuous intravenous drip. *Ann. Int. Med.* **30**:1295-1300, 1949.

88. Hagedorn, A. B., and Scheifley, C. H. Subacute bacterial endocarditis: case report. *Proc. Staff Meet., Mayo Clin.* **23**:14-16, 1948.

89. Eisman, S. H., Kay, C. F., Norris, R. F., and Boger, W. P. Caronamide as adjuvant to penicillin in treatment of subacute bacterial endocarditis. *Am. J. M. Sc.* **217**:62-70, 1949.

90. Stuart-Harris, C. H., Colquhoun, J., and Brown, J. W. Penicillin and caronamide in resistant subacute bacterial endocarditis. *Lancet* **1**:99-101, 1949.

91. Zweifler, B., Sar, E., and Feder, I. Subacute bacterial endocarditis due to *Streptococcus fecalis*. *Ann. Int. Med.* **34**:217-223, 1951.

92. Hager, R. P., Heitzman, E. J., and Young, R. M. Penicillin-caronamide therapy of enterococcus endocarditis. *Ann. Int. Med.* **34**:510-516, 1951.

93. Baker, G. P., and Pilkington, T. Benemid in treatment of streptococcal endocarditis. *Lancet* **2**:17, 1952.

94. Douthwaite, A. H. Benemid in treatment of streptococcal endocarditis. *Lancet* **2**:93, 1952.

95. Bundson, D. F. V., and Goulding, R. Benemid in treatment of streptococcal endocarditis. *Lancet* **2**:197, 1952.

96. Boger, W. P., Beatty, J. O., Pitts, F. W., and Flippin, H. F. Influence of new benzoic acid derivative on metabolism of para-aminosalicylic acid (PAS) and penicillin. *Ann. Int. Med.* **33**:18-31, 1950.

97. Boger, W. P., Matteucci, W. V., and Beatty, J. O. "Benemid" (p-[di-n-propylsulfamyl]-benzoic acid): lack of effect of aureomycin, chloromycetin, streptomycin and terramycin. *Proc. Soc. Exper. Biol. & Med.* **76**:222-225, 1951.

98. Dawson, M. H., Hobby, G. L., and Lipman, M. O. Penicillin sensitivity of strains of non-hemolytic streptococci isolated from cases of sub-acute bacterial endocarditis. *Proc. Soc. Exper. Biol. & Med.* **56**:101, 1944.

99. MacNeal, W. J., and Blevins, A. Bacteriological studies in endocarditis. *J. Bact.* **49**:603-610, 1945.

100. Schneierson, S. S. Serological and biological characteristics and penicillin resistance of nonhemolytic streptococci isolated from subacute bacterial endocarditis. *J. Bact.* **55**:393-399, 1948.

101. Selbie, F. R., Simon, R. D., and Robinson, R. H. M. Serological classification of viridans streptococci from subacute bacterial endocarditis, teeth and throats. *Brit. M. J.* **2**:667-672, 1949.

102. Finland, M., Wilcox, C., and Frank, P. F. *In vitro* sensitivity of human pathogenic strains of streptococci to seven antibiotics (penicillin, Streptomycin, Bacitracin, Polymyxin, Aerosporin, Aureomycin and Chloromycetin). *Am. J. Clin. Path.* **20**:208-217, 1950.

103. Levinson, D. C., Griffith, G. C., and Pearson, H. E. Increasing bacterial resistance to antibiotics: study of 46 cases of streptococcus endocarditis and 18 cases of staphylococcus endocarditis. *Circulation* **2**:668-675, 1950.

104. Hamburger, M., and Muething, D. *In vitro* sensitivity to eight antibiotics of streptococci and staphylococci recovered from cases of bacterial endocarditis. *J. Lab. & Clin. Med.* **37**:60-63, 1951.

105. Levinson, D. C., Griffith, G. C., and Pearson, H. E. Antibiotics in management of staphylococcal endocarditis with special reference to increasing bacterial resistance. *California Med.* **74**:167-170, 1951.

106. Ransmeier, J. C., Brown, H. E., and Davis, N. Comparison of in vitro sensitivity of freshly isolated pathogenic bacteria to terramycin and other antibiotics. *J. Lab. & Clin. Med.* **38**:620-630, 1951.

107. Dowling, H. F., Lepper, M., Caldwell, E. R., and Spies, H. W. Staphylococcic endocarditis: analysis of 25 cases treated with antibiotics, together with review of recent literature. *Medicine* **31**:155-176, 1952.

108. Spicer, S. Bacteriologic studies of newer antibiotics: effect of combined drugs on microorganisms. *J. Lab. & Clin. Med.* **36**:183-191, 1950.

109. Hunter, T. H. Speculations on the mechanism of cure of bacterial endocarditis. *J. A. M. A.* **144**:524-527, 1950.

110. Robbins, W. C., and Tompsett, R. Treatment of enterococcal endocarditis and bacteremia: results of combined therapy with penicillin and streptomycin. *Am. J. Med.* **10**:278-299, 1951.

111. Cates, J. E., Christie, R. V., and Garrod, L. P. Penicillin-resistant subacute bacterial endocarditis treated by combination of penicillin and streptomycin. *Brit. M. J.* **1**:653-656, 1951.

112. Jawetz, E., Gunnison, J. B., and Coleman, V. R. Combined action of penicillin with streptomycin or Chloromycetin on enterococci *in vitro*. *Science* **111**:254-256, 1950.

113. Jawetz, E., Gunnison, J. B., and Speck, R. S. Antibiotic synergism and antagonism. *New Eng. J. Med.* **245**:966-968, 1951.

114. Speck, R. S., and Jawetz, E. Antibiotic synergism and antagonism in subacute experimental streptococcus infection in mice. *Am. J. M. Sc.* **223**:280-285, 1952.

115. Jawetz, E. Antibiotic synergism and antagonism: review of experimental evidence. *Arch. Int. Med.* **90**:301-309, 1952.

116. Jawetz, E., and Gunnison, J. E. Experimental basis of combined antibiotic action. *J. A. M. A.* **150**:693-695, 1952.

117. Hunter, T. H. Use of streptomycin in treatment of bacterial endocarditis *Am. J. Med.* **2**:436-442, 1947.

118. Priest, W. S., and McGee, C. J. Streptomycin in treatment of subacute bacterial endocarditis: report of three cases. *J. A. M. A.* **132**: 124-126, 1946.

119. Keefer, C. S., and Hewitt, W. L. *The Therapeutic Value of Streptomycin: A study of 3000 cases.* 289 pp. Ann Arbor: Edwards, 1948. Pp. 62-65.

120. Wallach, R., and Pomerantz, N. Streptomycin in treatment of subacute bacterial endocarditis: review of literature and report of case caused by Bacteroides. *New Eng. J. Med.* **241**:690-695, 1949.

121. Olinger, M. G. Mixed infection in subacute bacterial endocarditis: report of two cases. *Arch. Int. Med.* **81**:334-341, 1948.

122. Loewe, L., and Eiber, H. B. Subacute bacterial endocarditis of undetermined etiology. *Am. Heart J.* **34**:349-365, 1947.

123. Suter, A. Penicillinresistenten Recidiv einer Sepsis lenta mit Streptomycin geheilt: ein kasuistischer Beitrag. *Schweiz. med. Wchnschr.* **78**:585, 1948.

124. Naegele, C. F. Streptomycin treatment of bacterial endocarditis due to *Streptococcus viridans:* report of two cases. *Ann. Int. Med.* **30**:1049-1053, 1949.

125. Luttgens, W. F. Endocarditis in "main line" opium addicts: report of eleven cases. *Arch. Int. Med.* **83**:653-664, 1949.

126. Friedman, I. A., and Goldin, M. Paracolon endocarditis. *Am. J. Clin. Path.* **19**:840-845, 1949.

127. Middleton, W. S. Streptomycin therapy of *Hemophilus influenzae* endocarditis lenta. *Ann. Int. Med.* **31**:511-513, 1949.

128. Love, J., Powell, C. P., Strunk, W. M., and Hinkens, G. F. Acute bacterial endocarditis of "Escherichia coli" origin: streptomycin treatment. *U. S. Nav. M. Bull.* **49**:1070-1075, 1949.

129. Aubert, A., and Lerche, C. Subacute bacterial endocarditis in child, ten months old, successfully treated with streptomycin. *Am. Heart J.* **39**:141-143, 1950.

130. Willcox, P. H. Streptomycin in subacute bacterial endocarditis: report of three cases. *Lancet* **2**:288-290, 1950.

131. Robbins, W. C., and Tompsett, R. Chronic recurrent nonhemolytic streptococcal endocarditis: report of patient treated concurrently with penicillin and dihydrostreptomycin. *Arch. Int. Med.* **86**:578-584, 1950.

132. Boynton, R. D. Subacute bacterial endocarditis caused by *Gaffkya tetragena:* report of case. *New Eng. J. Med.* **243**:738, 1950.

133. Harris, W. H., Jr., and Fishburn, G. W. Subacute Staphylococcus aureus endocarditis: recovery following combined antibiotic therapy. *Am. Heart J.* **43**:474-478, 1952.

134. Geraci, J. E. Antibiotic therapy of bacterial endocarditis. I. Experiences with terramycin in treatment of subacute bacterial endocarditis. *Proc. Staff Meet., Mayo Clin.* **27**:169-180, 1952.

135. Fritze, E., and Nasse, E. Ergebnisse der Behandlung der Endocarditis lenta mit Penicillin und Streptomycin. *Deutsche med. Wchnschr.* **77**:745-748, 1952.

136. James T. N. Enterococcal endocarditis. *Arch. Int. Med.* **90**:646-652, 1952.

137. Finland, M., Murray, R., Harris, H. W., Kilham, L., and Meads, M. Development of streptomycin resistance during treatment. *J. A. M. A.* **132**:16-21, 1946.

138. Murray, R., Kilham, L., Wilcox, C., and Finland, M. Development of streptomycin resistance of gram-negative bacilli *in vitro* and during treatment. *Proc. Soc. Exper. Biol. & Med.* **63**:470-474, 1946.

139. Cressy, N. L., Lahey, W. J., and Kunkel, P. Streptomycin in treatment of bacterial endocarditis: report of two cases. *New Eng. J. Med.* **239**:497-500, 1948.

140. Wright, S. S., et al. Antibiotic combinations and resistance to antibiotics. Development of resistance during repeated subcultures of staphylococci and certain streptococci on media containing penicillin, streptomycin, erythromycin, terramycin and chloramphenicol used singly and in pairs. *J. Lab. & Clin. Med.* **42**:877-895, 1953.

141. Finland, M., and Wilcox, C. Antibiotic combinations and resistance to antibiotics: penicillin with other antibiotics against penicillin-resistant staphylococci. *Proc. Soc. Exper. Biol. & Med.* **83**:605-608, 1953.

142. Editorial. Streptomycin and dihydrostreptomycin. *New Eng. J. Med.* **248**:1076-1078, 1953.

143. Lyght, C. E., and Hawkins, J. E., Jr. Streptomycin and dihydrostreptomycin in treatment of tuberculosis: comparative study. In *Transactions of the 12th Conference on Chemotherapy of Tuberculosis, February 9-12, 1953.* Washington, D. C.: Veterans Administration, 1953. Pp. 125-133.

144. Heck, W., and Hinshaw, H. C. Reduced neurotoxicity of mixture of streptomycin and dihydrostreptomycin. In *Transactions of the 12th Conference on Chemotherapy of Tuberculosis, February 9-12, 1953.* Washington, D. C.: Veterans Administration, 1953. Pp. 294 and 295.

145. Welch, H., and Lewis, C. N. Bacitracin. In *Antibiotic Therapy.* 562 pp. Washington, D. C.: Arundel Press, 1951. Pp. 123-137.

146. Bachman, M. C. *In vitro* studies on possible synergistic action between penicillin and bacitracin. *J. Clin. Investigation* **28**: 864-866, 1949.

147. Schwarz, L. H., and Lazarus, J. A. Unusual streptococcus from case of sub-acute bacterial endocarditis and its responses to combined penicillin bacitracin therapy. In *Proceedings of the Society of American Bacteriologists, May 14-18, 1950.* 151 pp. Baltimore, Maryland, 1950. Pp. 117 and 118.

148. Volini, I. T., and Kadison, E. R. Simultaneous bacitracin and penicillin therapy in subacute bacterial endocarditis: report on three cases. *Am. Pract. & Digest Treat.* **2**:13, 1951.

149. Welch, H., and Lewis, C. N. *Antibiotic Therapy.* 562 pp. Washington, D. C.: Arundel Press, 1951. P. 252.

150. Friedberg, C. K., and Bader, M. E. Acute staphylococcic endocarditis cured with aid of bacitracin. *J. A. M. A.* **147**:46-49, 1951.

151. Wallach, R., and Pomerantz, N. Combined antibiotic therapy: report of case of subacute bacterial endocarditis reinfected with diphtheroid and successfully treated with penicillin and bacitracin. *Arch. Int. Med.* **88**:840-846, 1951.

152. Zendel, J. F., and Lubart, A. Diphtheroid subacute bacterial endocarditis successfully treated with bacitracin. *Arch. Int. Med.* **90**:562-568, 1952.

153. Applebaum, E., Bruno, M. S., and Hochstein, E. Acute endocarditis as complication in bacterial pneumonia. *J. A. M. A.* **148**:93-98, 1952.

154. Loewe, L., Cohen, C., and Eiber, H. B. Factors in proper selection of antibiotic programs for cure of refractory case of subacute bacterial endocarditis. *Antibiotics & Chemother.* **3**:681-692, 1953.

155. Longacre, A. B., and Waters, R. M. Parenteral bacitracin in surgical infections. *Am. J. Surg.* **81**:599-606, 1951.

156. Meleney, F. L., and Johnson, B. A. Bacitracin. *Am. J. Med.* **7**: 794-806, 1949.

157. Zintel, H. A., Ma, R. A., Nichols, A. C., and Ellis, H. Absorption, distribution, excretion and toxicity of bacitracin in man. *Am. J. M. Sc.* **218**:439-445, 1949.

158. Meleney, F. L., Johnson, B. A., and Teng, P. Further experiences with local and systemic bacitracin in treatment of various surgical and nonsurgical infections and certain related medical infections. *Surg., Gynec. & Obst.* **94**:401-425, 1952.

159. Smith, L. W., Schultz, F. H., Jr., Ott,, W. L., and Payne, H. G. Comparative study of renal damage produced in mice by various lots of bacitracin. *J. Clin. Investigation* **28**:1018-1021, 1949.

160. Newton, G. G. F., Abraham, E. P., Florey, H. W., Smith, N., and Ross, J. Some observations on biological properties of bacitracins A, B and C. *Brit. J. Pharmacol.* **6**:417-429, 1951.

161. Schoenbach, E. B. Newer antibiotics: polymyxin, chloromycetin and aureomycin. *J. Mt. Sinai Hosp.* **16**:71-108, 1949.
162. Harvey, J. C., Mirick, G. S., and Schaub, I. G. Clinical experience with aureomycin. *J. Clin. Investigation* **28**:987-991, 1949.
163. Brainerd, H., et al. Clinical evaluation of aureomycin. *J. Clin. Investigation* **28**:992-1005, 1949.
164. Astler, V. B., and Morgan, H. R. Some biologic complications of prophylactic and therapeutic use of antibiotics. *Univ. Michigan M. Bull.* **16**:127-132, 1950.
165. Glaser, R. J., and Smith, D. E. Penicillin-resistant subacute bacterial endocarditis. *Am. J. Med.* **8**:794-804, 1950.
166. Merritt, W. A. Bacterial endocarditis as complication of transurethral prostatic resection. *J. Urol.* **65**:100-107, 1951.
167. Spies, H. W., Dowling, H. F., Lepper, M. F., Wolfe, C. K., and Caldwell, E. R., Jr. Aureomycin in treatment of bacterial endocarditis: report of nine cases together with study of synergistic action of aureomycin and penicillin in one case. *Arch. Int. Med.* **87**:66-72, 1951.
168. Hughes, S. O. Subacute bacterial endocarditis successfully treated with aureomycin. *Am. J. Med.* **10**:402-404, 1951.
169. Kane, L. W., and Finn, J. J., Jr. Treatment of subacute bacterial endocarditis with aureomycin and Chloromycetin. *New Eng. J. Med.* **244**:623-628, 1951.
170. Roberts, L. N., and Goldberg, W. M. Subacute enterococcal endocarditis. *Canad. M. A. J.* **65**:53-55, 1951.
171. Friedberg, C. K. Treatment of subacute bacterial endocarditis with aureomycin. *J. A. M. A.* **148**:98-103, 1952.
172. Donzelot, E., Kaufmann, H., and Castel, Y. Efficacité de la cortisone dans deux cas d'endocardite infectieuse à hémoculture négative. *Bull. et mém. Soc. méd. d. hôp. de Paris* **68**:57-59, 1952.
173. Flanders, J. F., McGee, L. C., and Scott, E. G. Enterococcal endocarditis: report of case treated with aureomycin. *Ann. Int. Med.* **36**:1323-1329, 1952.
174. Rubenstein, E., and Austin, P. G. M. Combined use of aureomycin and terramycin in treatment of subacute enterococcal endocarditis. *Am. Heart J.* **43**:922-926, 1952.

MEDICAL INTELLIGENCE

DOCTORS AFIELD

Joseph Warren

CHARLES H. BRADFORD, M.D.*

BOSTON

IT seems unfortunate that Joseph Warren is remembered so vaguely today, and that his associates are largely forgotten. Those who recall that Warren died heroically at the battle of Bunker Hill will perhaps fail to realize that he occupied, at the time, the position of the leading medical practitioner in Boston. Even fewer will appreciate the extent of his influence in the political field. Second only to Sam Adams, he organized, led and controlled the popular movement of resistance to British oppression. Together, they exercised such diplomacy, courage and skill that their efforts played a large part in precipitating the American Revolution. These three aspects of Warren's life — military, medical and political — are illustrated dramatically by his activities in the last twenty-four hours before he was killed, as related by his nephew, Dr. Edward Warren. Though unconfirmed, and possibly inaccurate, the incidents are characteristic enough to be worth repeating. On the night before the battle, it is known that he presided over the Provincial Congress, which met in Watertown. On the following morning, he is said to have attended an expectant mother; labor pains were slow, however, and he left the delivery to an assistant, after telling his patient that he must go to Charlestown "to get a shot at the British." Because of this medical call, it is supposed, he was late on the battlefield but not too late to refuse a major-generalship and fight as a private in the front line and not too late to stand fast when defeat overwhelmed his comrades and to meet death with unwavering defiance.

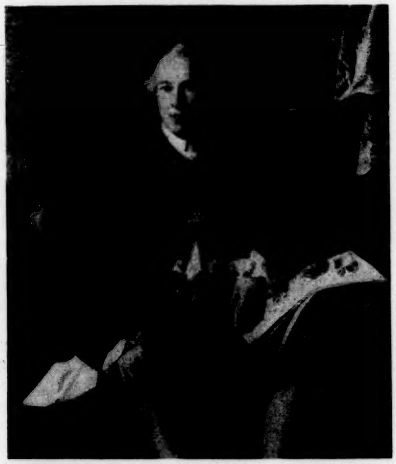
*Member of Orthopedic Staff, Boston City Hospital.

Warren began his medical career in 1760, under the tutelage of a prominent Boston physician, Dr. James Lloyd, who in turn had been trained in London with William Hunter. Since no medical school was available in Massachusetts before 1783, the apprentice system took its place during these earlier days. In some respects this method of teaching offered advantages that have never since been duplicated. Through it, the preceptor, in addition to dispensing his *knowledge*, could impart a share of his *wisdom*, which the pupil might not absorb in any other way. For the technical subjects, teaching was more than adequate. Compounding of drugs, for example, served as instruction in pharmacology in a way superior to any modern pedagogy. Substituting on calls, doing dressings, and covering minor emergencies gave the apprentice a graded sort of clinical experience that could hardly be surpassed. Didactic instruction came when he was accompanying the doctor on visits and discussing cases with him — equivalent to present ward teaching. Anatomy was learned by dissection, when and where possible. Body-snatching was the recognized method of obtaining anatomic subjects, since no legal method of obtaining bodies had been established.

In 1764 Warren, aged twenty-three, began practice for himself, rapidly advancing to eminence. A major reason for success lay in his extraordinarily appealing personality and character. His portrait, by Copley, now hanging in the Boston Museum of Fine Arts, shows a young man of a pleasing appearance, fair complexion, and athletic physique. His features tend to corroborate contemporary claims that he was the handsomest man in Boston of that day. Unfortunately, Copley seldom succeeded in catching an inward glimpse of the spiritual temper of his sitters. Here, the somewhat dull expression of the painting fails to suggest the fervor and intensity of Warren's emotions, or the lion-like courage that his actions demonstrated.

One of his outstanding characteristics was his rare, personal magnetism, which drew all men to him. He held, for instance, the intimate and con-

fident friendship of rigid, puritanical, John Adams and at the same time, shrewd, hard-headed Sam Adams loved him more than any other man. Even a man as remote in temperament as Benedict Arnold idolized the person and the memory of the great patriot. Still further evidence of Warren's unique capacity for evoking friendship was demonstrated by the commission he received in 1773 from the Grand Master of Masons in Scotland, appointing him the first grand master of all Masons on the American continent. Combined with this personal attractiveness, Warren possessed almost limitless energy. Up to the last few months, he seems never to have forsaken or neglected his professional duties. Only physicians, perhaps, can appreciate how absorbing the responsibilities of practice are. Yet on top of all these, Warren heaped an endless load of civic, social and patriotic activities that would have overwhelmed an ordinary man. Through the sternest trials he carried these tasks with a grace and charm of manner that never betrayed the irritations or frustrations of fatigue. Two other endowments gave Warren particular force: a clarity of intelligence that shone like a light through the perplexing problems of his time and a spiritual intensity that burned like fire in the face of oppressive dangers that most men would have shunned.



Joseph Warren, from the Portrait by John Singleton Copley (Reproduced with the Permission of the Boston Museum of Fine Arts).

Having won success in practice, Warren was generous in sharing it with the group of apprentices who soon applied to serve under him. They were men, in themselves, whose careers were to prove most interesting. One was Dr. Samuel Adams, son of the great political leader. Another was William Eustis, who served throughout the Revolution as an army surgeon and who eventually took up politics and finally became Governor of the State. John Warren, twelve years younger than his brother, was, from a medical standpoint, the most successful of his apprentices. He, too, served with the army in a number of campaigns, and then returned home in 1777 to direct a military hospital, which was located in a pasture, in the West End of Boston, close to the present site of the Massachusetts General Hospital.

In addition to these "apprentices," the contemporary associates of Joseph Warren formed an interesting group. Three in particular deserve mention. Dr. Bulfinch attracts notice only as a father of Charles, the great architect, who designed the Massachusetts General Hospital and the State House and who completed the design for the Capitol in Washington originally worked out by Hallet, Thornton and Latrobe. The father was a successful practitioner but something of an individualist. His charge for midwifery was 42 shillings, and he refused to join the Boston Medical Association, which regulated the fees of its members, because this organization set the charge exorbitantly at 48 shillings. Far more important in Joseph Warren's life was John Jeffries, a Boston man of about his own age, who had carried out his medical studies in London and then returned to practice in Boston. Because of his British affiliations, Jeffries remained a Tory, but this apparently did not disturb his personal relations with Warren. At Bunker Hill, Jeffries accompanied British officers immediately after the battle, and it was he who positively identified Warren's body before its hurried burial. Instant death had been caused by a bullet that shattered the skull. After the British evacuation of Boston, almost a year later, when the patriots' bodies were disinterred for reburial, another positive identification was required. It was carried out by Paul Revere, who was able to recognize his own handiwork in a tooth he had made for Warren.

An appraisal of Joseph Warren's political activities would require far more space than is permitted here. In general, his efforts may be divided into three major phases: as propagandist, as legislative-executive and as a man of action. In the first respect, he was tireless. Year in and year out, for a decade, his writings held the Tory leaders continuously on the defensive, and at the same time they cultivated and built up a spirit of patriotic enthusiasm among his compatriots. As early as 1768 Warren wrote such a convincing denunciation of Tory blunders and abuses that the Royal Governor, Bernard, in a fit of indignation dissolved the patriot legis-

lature because it had failed to suppress papers of this sort. At the height of the crisis, in 1774, Warren composed the masterly Suffolk Resolves. These were transmitted to Philadelphia for consideration by the first Continental Congress. The straightforward, hard-hitting language astonished that Assembly. "It is tantamount to a declaration of war," one of the more timid members objected. But its sentiments were expressed with such simple eloquence that they suggest the grand diction of the Declaration of Independence, which followed a year later. A brief sample deserves quotation:

> To us, our venerable progenitors bequeathed the dear-bought inheritance of liberty; to our care and protection, they consigned it; and the most sacred obligations are upon us to transmit the glorious purchase, unfettered by power, unclogged with shackles, to our innocent and beloved offspring ... In a cause so solemn, our conduct shall be such as to merit the approbation of the wise, and the admiration of the brave and free of every age and of every country.

Most impressive of all Warren's appeals was his oration in the Old South Church a month before the battle of Lexington and Concord. As one passes that building today, one can see the great window behind the pulpit where he made his entry. Because the hall below was too tightly jammed by the throngs of people to allow him passage, he came by ladder through the window. Three hundred British officers, in their scarlet coats, had gathered at the front of the hall to overawe and intimidate the Speaker. In fact, it was stated, on the authority of Hutchinson, that some of this group seriously considered assassinating Warren. Rumors also circulated that all the patriot leaders appearing here would be arrested and shipped to England for trial as traitors. This was, as a matter of fact, the intent of the British Ministry, but General Gage hesitated to carry it out, knowing the violence of public reaction that could be expected. It was here, on a similar occasion two years before, that Warren had coolly dropped a white handkerchief on the pistol of one officer who pointed it up at him. Again, thoroughly undaunted, Warren exhorted the Parliamentary leaders to desist, and warned Britain of the danger that would follow any further aggressions against the colonies. Unfortunately, his well reasoned arguments, like the great rhetoric of Edmund Burke, failed to penetrate the stolid stupidity of England's ruling class.

As a legislative-executive, Warren's achievements have passed more or less unnoticed, although they equal his other feats, and in some respects exceed them. It must be remembered that after the battle of Lexington and Concord, there was, as yet, no Declaration of Independence, and therefore, the Royal Governor still retained his full, executive powers. In the absence of any other legally constituted authority, government might easily have degenerated into mob rule. This was just what the Tories had predicted would follow in the wake of the revolutionary movement. The patriots avoided such a disaster by electing their own "congress," of which Warren was president, and by delegating its assumed powers to a committee of public safety, of which Warren was chairman. Thus, during the two months between Lexington and Bunker Hill, nearly everything that had to be done required Warren's initiative, Warren's judgment and Warren's decision. In this interval an army of 8000 undisciplined countrymen had assembled on the outskirts of Boston. They must be fed, sheltered, drilled and furnished with arms. Ammunition must be supplied. Tactical plans must be considered and approved. In addition the problems of the civilian population must be regulated: a large number of refugees from Boston must be housed and cared for; the support of communities ruined by oppressive British legislation must be provided; and order must be maintained. Public relations, especially with the other colonies, were of great importance and must be handled with extreme delicacy and tact. It is no exaggeration to say that all these problems came to Warren's hands, and with magnificent capability he met and overcame them, one by one. In two short months the rustic farmers and tradesmen were molded into elements of an army, rudely equipped and sternly, but willingly, sent to the great encounter at Bunker Hill.

Above all else, Warren preferred the role of action. His nephew states that he devoted part of every day to military exercises. He had often declared his willingness to die for the cause he held sacred. This seemed axiomatic with him. In one of his speeches he had asked characteristically, "When Liberty is the prize, who would shun the warfare; who would stoop to waste one coward thought on life?" This instinct for action did not grow unnaturally in Warren's character. As a small boy, he had heard his father remark, "I would rather my son were dead than that he should be a coward." His father's uncle had been captured in the Deerfield Indian massacre and was dragged all the way to Canada before his rescue. Such a background afforded no pacifist tradition or timid complaisance. It is small wonder, then, that when the first shots were fired at Lexington, Joseph Warren, who had the night before dispatched Paul Revere and William Dawes with messages of danger, should have hastened to engage in the combat. He was joined by his brothers, Eben, who came from Roxbury, and John, who hurried from Salem. With characteristic disdain for caution, Joseph exposed himself to the British fire so recklessly that a musket ball carried away a lock of hair that he wore in fashionable style over his ear. This close escape failed to teach him to take cover. It is reported that he engaged in every minor skirmish that took place up to the Battle of Bunker Hill.

From such venturous exploits, one might judge Warren to be a thoughtless firebrand who placed a low estimate on the value of life, — but this was far from true. His intellectual attainments, his literary skill and his scientific and medical training all belie the idea. By nature he was deeply religious, and his family attributed to him an unsurpassed knowledge of the Scriptures. His social position brought him friends in all walks of life. His family affairs were more than normally happy. He had married early, and was the father of four promising children. Tragedy interrupted this domestic joy when his wife died prematurely in 1773, but subsequently he became interested in Miss Mercy Scollay, and was thought to be engaged to her at the time of his death. Thus, having already won so much honor and success he was faced with no obstacle that could bar further progress toward everything a man might desire. In fact, as the historian Bancroft remarked, "the future seemed burdened with his honors." Why, then, did he needlessly, almost wilfully, and in spite of the protests of his friends, throw away his life in the first pitched battle? The question can bring only a conjectural answer.

One possibility is that he was carried away by the excitement of combat, as one of his friends had warned him would be the case. Perhaps, as often happens, the battle tensions that grip men under fire superseded his instincts of self-preservation. He himself had once expressed something of this inward fury. "They say we will not fight," he remarked, and added, "Would to Heaven I might die knee deep in their blood!" Or, possibly, with his keen political intuition and passionate devotion, Warren foresaw that the inspiring example of his courageous death would contribute more to the young and untested revolutionary cause than anything he could give it in life. Very probably it occurred to him that the banners of insurrection must be deeply colored in the red dye of mortal sacrifice before they could lead the crusade for human liberty to a triumphant end.

520 Commonwealth Avenue

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40091

PRESENTATION OF CASE

A forty-six-year-old male window dresser was admitted to the hospital because of fever and anemia.

Two years previously the patient had an attack of fever with cough, diagnosed as viral pneumonia, which subsided after treatment with chlortetracycline. One year before entry he had two short bouts of fever, which subsided spontaneously. Five months before admission he had a maximum temperature of 104°F., with weakness but without other symptoms. He was admitted to another hospital, where a chest film was said to have shown some abnormality. He was treated with chlortetracycline, and after about two weeks the fever subsided. Two weeks later, it recurred, again lasting about two weeks. This time he received penicillin. There were one or two shorter episodes of fever, which subsided without treatment. When fever again recurred two months before admission he was readmitted to the other hospital. At that time he had no complaints except the fever. The physical examination, blood counts and blood cultures were negative, and an electrocardiogram and a chest film were normal. A heterophil-antibody test and tuberculin skin test were negative. At one time there was some question of a "butterfly rash" on the face. One morning a large amount of red blood was found on his pajamas; internal hemorrhoids were discovered, and there was no other apparent source for the bleeding. An intravenous pyelogram and barium-enema examination were negative. He was treated with penicillin and Ilotycin, apparently without benefit. After about twenty days, during which he had occasional shaking chills, the temperature, which had ranged from 103 to 105°F., returned to normal. During his stay in the hospital eleven teeth were extracted. Soon after discharge from the other hospital fever recurred, the temperature rarely falling below 102°F., and he began to become anemic. There were still no other complaints of any kind. In the six months before admission to this hospital he had lost about 17 pounds in weight. He was referred to this hospital for further study.

The past history was noncontributory except for a hemorrhoidectomy ten years before admission. He denied exposure to tuberculosis or contact with wild or domestic animals. He had never traveled outside New England.

Physical examination, which showed a man who was somewhat drowsy and appeared febrile, was otherwise entirely negative.

The temperature was 103°F., the pulse 100, and the respirations 20. The blood pressure was 110 systolic, 60 diastolic.

The urine had a specific gravity of 1.018, and gave a trace test for albumin and sugar; the sediment was normal. The hemoglobin was 8.5 gm. per 100 cc., and the white-cell count 7500, with 66 per cent neutrophils and 28 per cent lymphocytes. The serum chloride was 80 milliequiv., the sodium 125 milliequiv., the potassium 3.0 milliequiv., and the carbon dioxide 32 milliequiv. per liter. The iron was 85 micromgm., the nonprotein nitrogen 21 mg., the total protein 4.8 gm., the albumin 2.6 gm., the globulin 2.2 gm., the total bilirubin 0.9 mg., and the alkaline phosphatase 5.8 units per 100 cc. Cephalin flocculation was + in forty-eight hours, and the prothrombin time was 55 per cent. Repeated blood cultures, aerobic and anaerobic, and a single urine culture were negative. The Widal test and agglutination test for brucellosis were each normal on two occasions. A Coombs test was also negative, as were intracutaneous tuberculin tests (first-strength and second-strength P. P. D.) and skin tests with histoplasmin and coccidioidin. A roentgenogram of the chest showed only some emphysema, and a plain film of the abdomen demonstrated two calcified bodies, perhaps lymph nodes, in the right lower quadrant of the abdomen and a third, perhaps a gallstone in the right middle portion. The tip of the liver lay at the level of the right iliac crest. An intravenous pyelogram was normal; there was no definite evidence of enlarged retroperitoneal lymph nodes.

In the hospital the patient was given transfusions, which increased the blood hemoglobin to 10 gm. per 100 cc. A sternal-marrow aspiration drawn on the day of the first transfusion was normal, with a myeloid-erythroid ratio of 4:1 or 5:1. Two L. E.-cell preparations were negative. An aspiration liver biopsy revealed no abnormality. A diagnostic lumbar puncture was completely normal, including the examination of the fluid. A concentrate of sputum was investigated for acid-fast bacilli, but none were found. Peritoneoscopic examination disclosed no abnormality.

Throughout the hospital stay the temperature remained at, or above, 103°F., only falling a little for the first few days after the beginning of streptomycin and PAS (para-amino-salicylic acid). The only complaint was weakness. On the twelfth hospital day the patient became confused, disoriented and tachypneic and thereafter seemed to fail rapidly. There were no positive neurologic findings. Rales at the lung bases developed, with x-ray evidence of increased bronchial markings and small patches of consolidation. Additional urinalyses were much as before. The highest white-cell count was 12,000; most ranged from 7000 to 10,000. By the twenty-fourth hospital day the patient's mental status had cleared somewhat; however, this change was only temporary. He became less and less responsive, and terminally respiratory difficulty developed. Death occurred on the thirty-seventh hospital day.

Differential Diagnosis

Dr. Robert L. Berg*: Can I safely assume that the liver did not appear enlarged on peritoneoscopic examination?

Dr. Edward B. Benedict: It seemed entirely normal.

Dr. Berg: We are faced with a patient who had anemia, fever and weight loss. In addition there was slight leukocytosis and a number of other questionable findings that are not very helpful; these include the possibility of a butterfly rash at some time, blood possibly from something other than hemorrhoids, an early chest abnormality during the admission to the other hospital, minimally abnormal liver tests, of which the prothrombin time was the most impressive, and enlargement of the liver noted on x-ray but apparently not on peritoneoscopic examination. These findings being of dubious value, the discussion must be based on the anemia, fever and weight loss. It is apparent that the differential diagnosis must lie among infection, cancer and connective-tissue disease. If in this situation on repeated culture no organisms are found, if there is no response to antibiotic therapy and if no biopsy showing malignant cells can be obtained, the convenient catchall diagnosis of connective-tissue disease is always ready.

All these widely different diseases produce a similar picture in the same way — by breaking down protein in the body. The host may contribute the destroyed protein from various types of abnormal host tissue. One type may be normal host tissue inherently affected by infarction. Other types include cancer as well as the products resulting from the reaction of host tissue to such slightly irritating invaders as the tubercle bacillus, which by itself contributes very little to the toxic reaction. The host reaction to this organism, on the other hand, may have a number of abnormal products. The foreign protein may arise from the invader itself, particularly from the endotoxins of bacteria. Finally, it may arise from the combination of host protein (antibodies) and the foreign invading substance as in allergic diseases, in which we think the connective-tissue diseases belong. It would be helpful if on a physiologic basis one could correlate clinical differences that were due to toxic manifestations of protein destruction with the type of protein destroyed, — infarcted host tissue, abnormal host tissue or invader tissue, — but we have very few clues in this direction. For instance, Dr. Wyman Richardson used to point out that if normal host tissue died, the differential blood count might

*Assistant physician, Massachusetts General Hospital.

show a lymphocytic predominance; with invader protein or with the antigen-antibody type of reaction, eosinophilia might be found. There are a few other slight differences, but they are of little help with this patient. Although I should like to approach this problem from a chemical and physiologic point of view, I see no way to do so, and I am forced to fall back on inadequate clinical information in trying to decide which of the general categories most closely fits this patient.

What we must consider is a relapsing illness with relatively symptom-free intervals but with increasing severity and finally death. Among the infections the relapsing illnesses are largely confined to the granulomatous diseases, in which there is substantially internal reinfection. The granulomatous agents are so slightly irritating that the body reacts indolently to them and finally encompasses them with a barrier and in a sense walls them off from the body for the time being. Among the granulomatous agents are the bacterial agents, primarily tuberculosis, syphilis and brucellosis, which may give similar histologic pictures. Whether or not there are viruses that produce generalized granulomatous disease we do not know. I think it likely that sarcoidosis will prove to be such a disease, and I like to speculate that beryllium intoxication may be merely a form of sarcoidosis to which beryllium ingestion predisposes. Finally, an uncommon disorder called cytomegalic inclusion disease, which has been observed infrequently in adults, may be of viral origin; in this disease there are typical granulomas and in addition a variety of inclusion bodies in cells filled with a large mass of cytoplasm. Under the protozoal infections I shall include histoplasmosis, coccidiomycosis and toxoplasmosis as the likely ones that need to be considered here. On the information given, there is no basis on which to choose among bacterial, viral or protozoal agents. One pertinent objection to all of them is that it is uncommon for any of these infectious agents to cause a relapsing illness in which the initial episode is mild, successive ones are more severe and closer together, and the most severe episode occurs after a long time.

In considering malignant growths I face the same problem. It is difficult to think of one in which the initial symptoms appear two years before death, are short lived and yet are severe, with a high fever, and are followed by a long period of quiescence. Of course, I may have to eliminate the first episode as a part of this disease, but it is in keeping with the further development. Among the tumors that could produce this situation are lymphoma, aleukemic leukemia and multiple myeloma. For the same reason that I eliminate infectious disease, I shall eliminate a malignant lesion. I do not eliminate it, however, with any satisfaction or assurance.

The most impressive factor about the case is the sequence of the clinical events to which I have already referred; whereas they are uncommon in cancer or in infection, they are, if not characteristic, at least not rare in connective-tissue disease. The sequence of events, although consistent with a recurrent disorder, unfortunately gives me no localizing help. The fact that nothing else developed in the body in the course of this disease is equally against all diagnoses. One would expect that, with any of these conditions, other signs or symptoms would have appeared as death approached. In this case I should say that the disorder was within the triangle at whose corners are lupus erythematosus, rheumatic fever and rheumatoid arthritis. One might say it was rheumatic fever without rheumatism or lupus erythematosus without any of the three findings that we used to consider necessary for the diagnosis — namely, splenomegaly, leukopenia and kidney disease. There was nothing to suggest rheumatoid arthritis. Although the diagnosis is a totally unsatisfactory one in terms of specificity, I feel happier with connective-tissue disease than with either cancer or infection in view of the chronologic sequence, and I shall not try to be more specific than that.

DR. WILLIAM H. BAKER: Do you think the type of fever that the patient had might be helpful in determining the type of illness? This is the type of fever noted with Hodgkin's disease — the so-called Pel–Ebstein fever.

DR. BERG: Yes; it is slightly helpful.

DR. JOSEPH C. AUB: I saw this patient once and I did not know what he had. As a matter of fact I thought he was cheating on the temperature and therefore took it with a finger on the thermometer. He did have a fever. I thought he might have lymphoma. I left the case without any satisfaction or assurance about the diagnosis.

DR. BENJAMIN CASTLEMAN: Dr. Ropes, what do you think about connective-tissue disease in this patient?

DR. MARIAN W. ROPES: My opinion about the fever is different from Dr. Berg's. This type of fever, with such sudden shifts, is relatively unusual in the so-called connective-tissue diseases. I agree, however, that nothing pointed in any direction. I think I should have felt happier choosing the lymphoma group than the connective-tissue group.

DR. BERG: I should like to ask Dr. Aub if the acute spikes of temperature are seen with lymphoma with such wide intervals between attacks.

DR. AUB: Yes; it is suggestive of the disease.

This is a good example of the difference in point of view of the clinician caring for a patient and the discusser trying to make a diagnosis at a clinicopathological conference. The discusser is not concerned with any therapeutic procedure; the clinical consultant is called to decide what should be done

next for the patient. If I had known that this man was going to die in a few days, I should have recommended x-ray therapy without knowing the diagnosis, but I did not know that. If the fever did result from lymphoma he must have had involved retroperitoneal lymph nodes, but it did not seem worth while to do an exploratory laparotomy to remove one.

DR. CASTLEMAN: That is why peritoneoscopic examination was performed. Dr. Benedict, will you tell us about it?

DR. BENEDICT: We examined him endoscopically with the idea of possibly finding tuberculous peritonitis; I think we ruled that out as well as possible carcinomatosis. We could not rule out lymphoma; that is often retroperitoneal so that we cannot be sure he did not have lymphoma. Some physicians said he had ascites; we did not find any.

DR. C. C. WANG: The intravenous pyelogram gave no evidence of enlarged retroperitoneal lymph nodes.

DR. JACOB LERMAN: How can you rule out retroperitoneal lymphoma by means of the intravenous pyelogram?

DR. WANG: Sometimes the lymph nodes press on the ureter, indicating that they are enlarged. Negative findings naturally do not exclude enlargement.

DR. CASTLEMAN: I should imagine that the lymph nodes would have to be over 5 cm. in diameter to cause a displacement of the ureter.

DR. HOWARD ULFELDER: I should like to ask Dr. Berg if he would consider more seriously carcinoma of the stomach or pancreas.

DR. BERG: Now that you have raised the point I am sure it should be considered. Again, let me ask the same question, Do you think, with such diseases, the temperature rises so high?

DR. ULFELDER: Yes; I have seen a similar level in carcinoma of the cervix, pancreas and stomach.

DR. BERG: With such long intervals between attacks?

DR. ULFELDER: That is the most surprising thing about this case. The patient had something very serious the matter with him; that is why I keep going back to cancer.

DR. ALFRED KRANES: If Dr. Berg had difficulty with this problem you can imagine the troubles of the clinicians who were caring for the patient. When I first saw him at the suburban hospital, he was recovering from one of his febrile episodes, and I later saw him on one or two occasions after his admission here. It was hard to know whether the initial episode of fever, two years before admission, bore any relation to the present illness. We explored the same ground that Dr. Berg did and tried to get evidence of one or the other of the diseases mentioned but none was forthcoming. When I saw him on admission to this hospital, there was a striking change in his appearance. Whereas several months before he had not appeared ill, he now looked mortally sick. It was apparent that if something were not done he was going to die. It seemed improbable to me that a patient could be so near death from cancer without some slight evidence of it either on repeated physical examinations or on laboratory tests. The one disease that might be likely to escape detection for so long and give no physical signs was miliary tuberculosis. I therefore suggested that the patient be given streptomycin and PAS to see what would happen. For forty-eight hours I was a minor prophet on the ward because the temperature came down and he began to feel better, but unfortunately not for long.

DR. BERG: Had you believed that the attacks two years previously were unrelated?

DR. KRANES: Yes.

DR. H. TREVOR COOKE: I should like to ask if any correlation might be found among the low serum potassium, the PAS therapy and some of the features of the terminal illness, which could very well fit in with hypokalemia as the secondary effect.

DR. BERG: I should guess that if the serum potassium determination had been repeated later, it would have been normal. On admission the patient was rather desalted; efforts were undoubtedly made to restore the salt values to normal.

A PHYSICIAN: He was given intravenous therapy, and the electrolytes returned to normal in the terminal part of the illness; an effort was made to restore the caloric intake as well as the electrolyte disturbance. I do not recall the final chemical levels, but we thought that did not contribute a great deal to his death.

DR. CASTLEMAN: Dr. Palmer, what did you think this patient had?

DR. ROBERT S. PALMER: I thought a fair possibility was visceral tuberculosis. At one point the question came up, Should he be explored to biopsy a pelvic or retroperitoneal lymph node? We settled for therapeutic tests and the peritoneoscopic examination, and we got no help from either.

DR. BERNARD M. JACOBSON: The summary of this record did not make any mention of size or shape of the red blood cells. The cells were normocytic, with very little variation in size and shape; in other words, this was the picture of the simple chronic anemia seen in a large variety of infectious and neoplastic diseases. The aspiration of the bone marrow was certainly a good step, but we should remember that in cases of fever of unknown origin, without immature cells in the peripheral blood, the chances of finding anything diagnostic in the bone marrow are slim, and only in the unusual case of metastatic cancer are malignant cells observed in the bone marrow. The bone-marrow aspiration was not diagnostic in this case. Like Dr. Kranes, I thought that this was miliary tuberculosis.

Clinical Diagnosis

?Lymphoma.
?Miliary tuberculosis.

Dr. Robert L. Berg's Diagnosis

Connective-tissue disease.

Anatomical Diagnoses

Malignant lymphoma, Hodgkin's type, involving retroperitoneal lymph nodes, bronchial lymph node, liver, spleen and bone marrow.
Bronchopneumonia.

Pathological Discussion

Dr. Castleman: The bone-marrow biopsy that had been done a week or ten days before the man died was examined and re-examined many times. We described the marrow as being very unusual; there were no fat cells, and there were many eosinophils — a granulomatous type of reaction. There were multinucleated cells, but often in a marrow such cells are megakaryocytes. It would be difficult from an aspiration or small biopsy of bone marrow to determine whether multinucleated cells were Reed-Sternberg cells of Hodgkin's disease or megakaryocytes. We could not find anything to suggest a tubercle, although it is well known that tuberculosis when it involves the bone marrow may not present the characteristic tubercle. We finally wrote a long note saying that we could not rule out Hodgkin's disease.

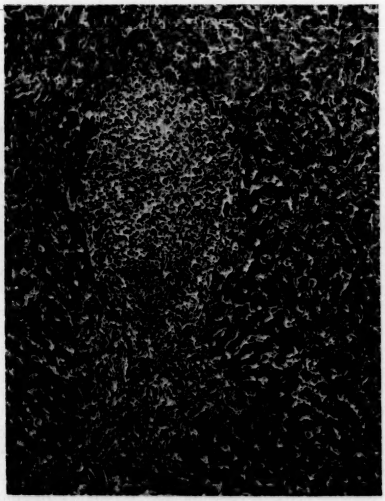


Figure 1.

At the time of autopsy the liver seemed perfectly normal, but was a little larger than normal, weighing 2400 gm. The spleen was enlarged to about twice the normal size, weighing 400 gm. We found enlarged retroperitoneal lymph nodes measuring up to 3 to 4 cm. along the abdominal aorta all the way up to the diaphragm. They were moderately firm and on section presented an appearance not unlike that of malignant lymphoma; they were grayish white and homogeneous. One bronchial lymph node in the carinal angle showed a white spot, but all the other lymph nodes in the chest were quite anthracotic and looked perfectly normal. The lungs were emphysematous and contained small areas of pneumonia, especially in the left lower lobe.

On microscopical examination the retroperitoneal lymph nodes presented a characteristic picture of Hodgkin's disease. The white spot in the bronchial lymph node also showed Hodgkin's disease; this was the only other lymph node involved. This patient had had two liver biopsies that were perfectly normal; the autopsy sections, however, demonstrated widely scattered, microscopic foci of Hodgkin's disease (Fig. 1). They were not too numerous, and it would have been only chance to have included one in a needle biopsy. All sections of the bone marrow were extensively diseased. Most of the marrow was composed of areas that were not unlike those we saw on the ante-mortem bone-marrow biopsy. In retrospect there is no doubt that this was Hodgkin's disease in the biopsy. It is interesting that the number of Sternberg cells is so much smaller in the marrow than in the lymph nodes or anywhere else.

CASE 40092

Presentation of Case

An eleven-year-old boy was admitted to the hospital because of pleuritic pain and fever.

The patient had been well until about three weeks before admission, when, while playing football, he was knocked down, falling on his left side. He got up and continued playing, however, with little discomfort. Later in the game one of his friends was hurt, and the patient took his friend home. While there he vomited, was taken to his own home and vomited several more times. By evening, however, he was asymptomatic except for a mild "stomach ache." On the following morning he was completely without symptoms. He felt completely well and carried on full activity for about a week after the football game. At the end of that time he began to experience sharp left-upper-quadrant pain, which he felt when he took a breath. The pain lasted only

seconds and bothered him more at night. Several days later he noted pain in the anterior part of the left shoulder on deep breathing. This pain was described as knife-like, did not occur with each respiration and never awoke him from sleep. During this time he had a low afternoon fever, the temperature rising to 100 to 101°F. by mouth. The morning temperature was normal. He was started on chlortetracycline, receiving 600 mg. in six days without change in temperature pattern or symptoms. A week before admission fluoroscopic examination revealed an 8-cm. mass in the region of the spleen displacing the stomach medially. The mass could not be palpated, and there was no tenderness in the area. Antibiotic therapy was changed to Biosulfa (penicillin, sulfadiazine and sulfamethazine), but there was no real improvement. Four days before admission a second fluoroscopic examination failed to demonstrate the mass previously visualized. Three days later a maximum temperature of 103°F. developed, and the patient was referred to this hospital for study.

The past history was negative for severe injuries or illnesses.

Physical examination revealed a pale and thin boy. When first seen he was vomiting and complaining of feeling faint. The heart and lungs were normal. The abdomen was poorly relaxed; however, the spleen was palpated two fingerbreadths below the costal margin. Once during palpation of the spleen, he complained of shoulder pain. The examination was otherwise negative.

The temperature was 100.2°F., the pulse 120, and the respirations 18. The blood pressure was 110 systolic, 80 diastolic.

A urinalysis was normal. Examination of the blood disclosed a hemoglobin of 12.8 gm. per 100 cc. and a white-cell count of 13,000, with 79 per cent neutrophils.

In a roentgenogram of the chest, the left leaf of the diaphragm was somewhat higher than the right. A plain film of the abdomen showed questionable enlargement of the spleen. There were no rib fractures, and no fluid in the peritoneal cavity. A gastrointestinal series demonstrated serrations along the lateral superior portion of the stomach at the point of contact with the superior portion of the spleen (Fig. 1). The psoas-muscle shadow was normal, as was the outline of the inferior part of the spleen.

Left-upper-quadrant and shoulder pain persisted. An operation was performed on the third hospital day.

Differential Diagnosis

Dr. Lamar Soutter*: May we see the x-ray films?

Dr. Joseph Hanelin: The films of the chest and abdomen were made on the day of admission, and an examination of the stomach on the next day. There is slight elevation of the left leaf of the diaphragm. Even the chest examination indicates enlargement of the spleen, chiefly of its upper pole. In the abdominal film there is evidence of splenic enlargement, the upper pole of the spleen being more bulbous and larger than the rest. The psoas-muscle shadows are clearly demarcated, and there is no suggestion of increase in free intra-abdominal fluid. The gastrointestinal series shows a fairly prominent impression on the fundus of the stomach by what was considered to be a large spleen (Fig. 1); other films also demonstrate the splenic enlargement,

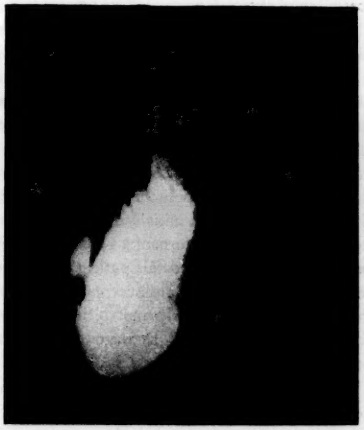


Figure 1. *Roentgenogram from the Gastrointestinal Series, Showing Indentation on the Lateral Posterior Aspect of the Fundus of the Stomach by the Enlarged Upper Pole of the Spleen.*

which appears to be greater at the upper pole. The mucosal markings are accentuated along the greater curvature of the stomach.

Dr. Soutter: This is a picture of trauma with delayed consequences in a preadolescent child. In considering an injury in the left upper quadrant, we think of a rupture of the diaphragm, stomach, colon, kidney, adrenal gland, tail of the pancreas, liver and lastly, but most often, the spleen. I think I can promptly eliminate most of these. The contour of the diaphragm was round and smooth in all the x-ray films. There was very little fluid and no obvious blood in the chest cavity, and the stomach was in a normal position; these findings rule out a ruptured diaphragm. Rupture of the stomach or colon is generally followed by a fairly acute and severe course, not a prolonged one such as this patient had. Rupture

*Associate professor of surgery, Boston University School of Medicine.

of the stomach nearly always produces bloody vomitus, peritonitis and shock. Similarly, rupture of the colon results in intraperitoneal sepsis and intestinal dilatation, which were absent. We can, therefore, eliminate these possibilities.

Rupture of the adrenal gland is extremely rare without severe damage to surrounding organs. A rupture or tear of a kidney with a hematoma is usually accompanied by hematuria and dysuria. If a febrile course ensues, it usually means that there is a perinephric abscess, which can be diagnosed by the localizing signs, particularly pain and tenderness in the costovertebral angle. We can disregard the possibility of severe damage to those organs.

Pancreatic damage occurs after severe trauma, which is inflicted more medially than this boy's was. It may result in some local necrosis and eventually the presence of a false or true cyst of the pancreas. Such a cyst is usually medial and displaces the stomach anteriorly and to the left. With rupture of the left lobe of the liver, there is bleeding and extravasation of bile into the peritoneal cavity, with signs of shock and peritonitis initially. If the damage to the liver had been in the form of a subcapsular hematoma, it could have caused this patient's symptoms. The enlarged left lobe of the liver, however, should press the stomach anteriorly and to the left instead of downward and medially. Damage to these organs is therefore unlikely.

We are probably safe in considering the spleen as the organ most likely to have been injured. In left-upper-quadrant trauma it is the organ most frequently implicated, and the trauma need not be severe to have dramatic results. Was there some abnormality of the spleen that rendered it more susceptible to injury? Nothing in the patient's course before injury makes us think that there was evidence of cancer. Nothing in the recorded blood findings suggests a hematologic abnormality. The possibility of an infectious process, such as mononucleosis, in which the spleen is known to rupture readily, seems slight. The boy was perfectly well at the time of the injury. Amyloidosis and similar conditions in which this organ ruptures readily need not be considered in a healthy boy. It is possible that he had a congenital cyst of the spleen that was damaged. Cysts are rare, but are commoner in children than in adults. There was no history of previous splenic enlargement, and yet he must have had physical examinations at school. Furthermore, the association of acute trauma and splenic cysts is rare.

Trauma to the spleen usually results in either single or multiple lacerations or causes the organ to be split or even avulsed from its pedicle. Signs of peritoneal irritation and hemorrhage are often immediate. There are, however, a number of cases recorded in the literature in which signs of hemorrhage and shock have been delayed. Zabinski and Harkins,[1] who reviewed the literature and reported their own cases, found that 14 per cent of the patients with ruptured spleens had delayed bleeding. Of this group of 63 patients with delayed rupture, in 55, or 87 per cent, the interval before the signs appeared was five hours to sixteen days after the initial damage; in the remaining 8 patients the time varied up to two years. A three-week delay is unusual, therefore, but not impossible.

If this child had had an acute laceration with bleeding into the peritoneal cavity he would originally have had signs and symptoms of shock — a rigid abdomen and localized pain and tenderness in the left upper quadrant. Since these were apparently missing either the bleeding was slight or confined to the subdiaphragmatic area with prompt clotting, or else a splenic hematoma developed—in other words, he had subcapsular hemorrhage. Subcapsular hemorrhage, of course, is somewhat unusual, but a number of cases have been reported in the literature; the patients have few signs or symptoms initially, but changes may develop as time goes on, as in the case under discussion.

There is a possibility of torsion of the spleen, with infarction. Torsion of the spleen, which is rare, occurs in the so-called wandering spleen, which has a long pedicle permitting it to descend low into the abdomen or even into the pelvis. This boy's signs and symptoms, particularly the long-standing fever, are consistent with an infarction, but the fact that the spleen remained in the left upper quadrant is against its having rotated on a long pedicle.

Could a subphrenic abscess have developed from a hematoma that had become infected by a hematogenous spread of bacteria? A subphrenic abscess is accompanied by fever and localized pain. There would have been associated fluid in the chest cavity at the time of admission, for by then the abscess would have been of long standing. I doubt very much if he had a subphrenic abscess.

Would a laceration or subcapsular hematoma have produced vomiting? It could have. In the Boston

Children's Hospital series of 7 cases of acute splenic rupture[2] 6 patients had nausea and vomiting. What about fever? The temperature in the case under discussion was higher than that in any of the cases of delayed hemorrhage or hematoma reported by Zabinski and Harkins.[1] Their patients rarely had a temperature over 101°F. — this child allegedly had a temperature of 103°F. on the day before entry. How do the x-ray findings fit into this diagnosis? The fact that the psoas-muscle shadows were so clearly seen tends to rule out retroperitoneal hemorrhage or peritonitis. The barium-swallow study of the stomach, which revealed a lateral indentation of the fundus with serrations, is consistent with splenic trauma. That finding is frequently present when the spleen is ruptured. Kerr's sign — diaphragmatic irritation and pain referred to the shoulder — occurs in varying frequency after splenic rupture; it is probably present in less than half the reported cases. Pressure on the spleen has been observed to produce shoulder pain after splenic trauma. Both these signs were present in this child.

In conclusion, I think that the spleen was damaged by the fall, and that it bled beneath the splenic capsule, forming a hematoma. If blood was found in the peritoneal cavity at operation, it was small in amount.

DR. JOHN D. CRAWFORD: The histories given at the time of admission, although they contained the same facts given in the protocol, placed the emphasis on fever and the possibility of infection. The fact that the patient was not operated on for thirty-six hours after admission was due to that emphasis; the possibilities of rheumatic fever and infectious mononucleosis came to mind. The episode of trauma, which was the point emphasized in the protocol, was almost forgotten in the story told on admission.

CLINICAL DIAGNOSIS

?Ruptured spleen.

DR. LAMAR SOUTTER'S DIAGNOSIS

Rupture of traumatized spleen, with subcapsular hematoma.

ANATOMICAL DIAGNOSIS

Trauma to congenital cyst of spleen, with intracystic hemorrhage.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At operation, Dr. E. Stanley Crawford found a large spleen, whose upper pole was made up of a cystic mass about 12 cm. in diameter that was slightly adherent to the diaphragm. There was no free blood in the abdominal cavity. This cyst was filled with old, chocolate-colored blood; its lining was fairly smooth and trabeculated and did not suggest organization of a hematoma. Microscopically, the wall was thick, and its inner surface was composed of epithelium that in places was pseudostratified. I do not believe that this type of lining cyst could have resulted from organized hemorrhage over a three-week period. We interpreted this as a congenital cyst of the spleen, which is sometimes called an epidermoid cyst, not a dermoid cyst, since it does not contain sebaceous glands or hair. The most common type of true splenic cyst is a lymphangioma, but there was no evidence of that here. I suppose that when the patient fell, the inner wall of the cyst was injured, with hemorrhage into the cystic cavity itself.

DR. WALTER BAUER: Are the cysts more frequently in the lower pole?

DR. CASTLEMAN: According to Fowler,[3] who reviewed the literature on this subject, they appeared to be about three times more common in the lower pole than in the upper, probably because most splenic cysts are traumatic in origin (false cysts) and the lower pole is more likely to be injured.

REFERENCES

1. Zabinski, E. J., and Harkins, H. N. Delayed splenic rupture: clinical syndrome following trauma: report of 4 cases with analysis of 177 cases collected from literature. *Arch. Surg.* 46:186-213, 1943.
2. Scott, H. W., Jr., and Bowman, J. R. Traumatic rupture of spleen in childhood. *J. A. M. A.* 130:270-273, 1946.
3. Fowler, R. H. Cystic tumors of spleen. *Internat. Abstr. Surg.* 70:213-223, 1940.

Correction: The name, "Dr. Mary N. McGovern," in the fifth paragraph of the right-hand column on page 219 of the February 4 issue of the *Journal* should have been "Dr. Joseph J. McGovern."

The New England
Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
AND
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. Richard E. Alt, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR
James F. Ballard, BOOK REVIEW EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
C. Guy Lane, M.D. Vernon P. Williams, M.D.
Henry R. Viets, M.D. Benjamin Castleman, M.D.
Robert M. Green, M.D. Hugh R. Leavell, M.D.
Dwight O'Hara, M.D. J. Englebert Dunphy, M.D.
Fletcher H. Colby, M.D. Robert W. Buck, M.D.
Robert L. Goodale, M.D. Herrman L. Blumgart, M.D.
Chester M. Jones, M.D. Frank N. Allan, M.D.
Harvey R. Morrison, M.D. Harvey A. Kelly, M.D.
Maxwell Finland, M.D. Langdon Parsons, M.D.
Deering G. Smith, M.D.*

*Representing the New Hampshire Medical Society.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (first-year interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

TEACHING OF SURGICAL TECHNIC

THE teaching of surgeons in the postgraduate phase — during an internship-residency period — involves a dimension not so clearly evident in the instruction of the young physician. Consideration of this added dimension in surgical education, usually included under the term "surgical technic," has recently come to the fore because of new problems posed in this day of a dwindling ward population.

There seem to be two schools of thought. One maintains that, after all, surgical technic is not difficult to learn and that it is a matter of little moment. It is easily taught, and it forms the least difficult aspect of surgical residency education. This view is well presented by the Committee on Graduate Surgical Education of the American Surgical Association, the report of which, recently published in the *Annals of Surgery*, states in part:

> Experience indicates that it is relatively easy for the young surgeon to obtain technical competence. Those who elect a surgical career gain a satisfaction from operating. Older surgeons like to demonstrate their skill. What with students' yearning and teachers' inclination, the training aspect of the surgeon's upbringing needs little urging.

The other opinion holds that the teaching of technical surgery is a matter of some difficulty, particularly since it involves a transference of vital responsibility to an inexperienced person; and that besides manual dexterity, intelligence, wisdom and mercy are mingled in the surgical act.

This view is in part exemplified by the recent report of the New England Surgical Society. This document, although primarily concerned with economic forces in surgical education, makes clear the deep concern of the committee members that the teaching of technical surgery is a matter not to be entered into lightly, being one in which many problems are unsolved and urgency for solution is great. The report, read before the Society last fall, raises certain economic and ethical questions that point up this view. It asks the question, "Can a surgeon ethically turn over all or part of an operation on one of his private patients to a member of the resident staff for teaching purposes?" The very fact that the report asks such a question and goes to some pains to answer it indicates that in the minds of the authors the teaching of surgical technic is a serious problem.

It is not the purpose of this editorial to discuss the private patient and his relation to surgical teaching, important though such questions may be, but rather to bring into focus just what is meant by "surgical technic." Is this something, indeed, that is easy to teach, a mere piece of manual training for which the students yearn and the instructor shows off? Or is it a matter of such seriousness and difficulty that it is today in jeopardy?

Like many differences of opinion this one is traceable to a definition. If "surgical technic" is defined as comprising only the petty digital minutiae of surgery, it is obviously easy to teach and one could scarcely take issue with the report of the American Surgical Association. How is the scalpel held? At

what precise angle are the scissors deployed for cutting a suture? How deep should the first incision go? When does one clamp and ligate the bleeding vessels? Is an intestinal clamp removed before or after the anastomosis? Whose clamps clamp best, and whose snaps snap the snappiest? If these details constitute surgical technic, one will agree that they are easy to teach. Some men are talented in these regards, and others are not. But in general, this is not a difficult problem in pedagogy.

Unfortunately, the view that this class of petty detail is at the heart of surgical technic is not shared by all.

Surgical technic is best exemplified by the story of a senior professor in surgery on a certain morning about fifteen years ago as he approached a difficult pulmonary resection. From the first moment that he entered the hospital, his mind was on the operation, many of whose technical aspects he had been considering for many days, as well as throughout the previous evening. His schedule for the day was built around this operation, which was not merely crammed into a hurried run of visits, other surgery and committee meetings. The resection proceeded not grimly or desperately but calmly, dexterously, purposefully and by masterful design. Some features of the case unexpected to the rest of the team were taken in stride by the surgeon, who had considered them as possibilities and was prepared for them. The adaptation of the operative procedure itself, as a technical act, to the age of the patient, to his occupation and to the histology of the neoplasm proved by frozen section, was as integral a part of this operation as the sharpness of the scissor or the angle of the scalpel. The anesthetic used, the methods chosen to maintain adequate ventilation and the details of the incision, its closure and the postoperative care were all welded into an effective demonstration of surgical technic at its greatest.

One must emphatically agree with the concept that this kind of surgical technic is not easy to teach. It involves deep responsibility for the patient as well as the three-dimensional visualization of pathology. It involves a knowledge of man and disease, as well as shiny sterile weapons. There is, to be sure, an aspect of manual dexterity, but it has generally been overrated. The mental process that accompanies a successful surgical operation has been underrated. Any attempt to separate "surgical technic" from the totality of the surgical operation leads to the concept that a man might be trained to be a good technician while yet a poor surgeon, whereas by any reasonable classification a man who does poorly by his patient at the operating table is a poor exponent of surgical technic and must be regarded as a poor technician no matter how flashy his handling of the knife.

It is suggested, therefore, that for purposes of teaching the term "surgical technic" be dropped, and "surgical operation" be used instead. Safe and effective conduct of the surgical operation in a manner adapted to the patient's needs is the objective in technical teaching.

There is a deplorable tendency to regard the mere teaching of the surgical operation as something that is below the dignity of an educator, who should be much more concerned with psychiatry, social service, biochemistry or physiology. This unfortunate state of mind arises from much too narrow a definition of the technical aspects of surgery. When it is put into its proper frame of reference, and the act of surgery is defined as the surgical operation and everything that pertains to it, it looms as one of the most important, if not the most important, single events in the care of the surgical patient.

Indeed, most of the unnecessary surgical morbidity and mortality in this country today arises from poor teaching of the surgical operation itself. The patient's duodenal stump may have been closed with large sutures that choked off all the blood supply so that three days later it blew out and he died: although his duodenal ulcer may have had psychiatric implications, this is what killed him. Or the common duct may have been divided, or the ureters included in the hysterectomy clamp. Or the blood loss may have proceeded at the pneumonectomy more rapidly than replacement, so that the patient died of shock. Or possibly the patient should not have been operated on that morning at all but should have been allowed a few more days of rest in the hospital. All of this centers around the surgical operation, and none of it is easy to teach. It takes years. It takes planning. And above all it takes conscientiousness and honesty on the part of the instructor, and the ability of the student to assume responsibility.

To focus the teaching of technical surgery on the operation as a whole rather than on its technical minutiae in so sense minimizes the importance of the many other aspects of the "sum total of means" — metabolism, biochemistry and physiology:

> An operation should be viewed as an extremely important tactical feature of a broad plan to get a patient well. When placed in this light the term "pre and postoperative care" begins to lose its significance. Surgical care is a unified entity ... and its effectiveness to the patient lies in the tremendous scope of the concepts brought to bear on the problem at hand. Success may hinge equally on a well-tied knot or on a thorough understanding of the biochemistry of the obstructed nephron.

One can most certainly agree with the members of the committee of the New England Surgical Society who state in essence that the granting of this teaching responsibility is becoming increasingly difficult in hospitals today, especially in smaller communities, where private practice dominates the scene. This problem is here to stay. Its solution will not come through any single pattern. It is of the greatest importance that the medical societies and the Blue Cross and Blue Shield corporations realize that it is in the long-term interest of the public to aid in teaching surgeons by helping to solve the problem of technical teaching on private wards, which, despite its importance, has not been the main concern in this discussion.

The purpose is rather to emphasize what it is that is being taught in technical surgery. The objective centers around surgical technic, but that term has become meaningless through too narrow a definition. The whole problem is the teaching of "the surgical operation." When the matter is so stated, it becomes apparent that something of profound importance to the patient is being taught, that success requires special qualities of intellectual honesty as well as digital dexterity, that the teaching must penetrate far beyond the manual-training level and that it is certainly far more important to the patient and to the educational program than learning how to hold a knife with the little finger deftly extended in anticipation of the stroke.

Surgical technic is something apart; it can be considered and studied apart from the patient. The surgical operation can never be considered apart from the patient. It is conceived as specific therapy for specific disease and dedicated to the betterment of a man, woman or child. In hospital teaching one is much more concerned with the operation so conceived and so dedicated than with the technical minutiae that go to make it up.

TELECASTS ON CANCER

As is generally known in the local area, an interesting series of telecasts for the professional education of physicians is being shown in the Jimmy Fund Auditorium of the New England Children's Medical Center. It is sponsored by the American Cancer Society and its Massachusetts Division, with the co-operation of the Columbia Broadcasting System.

On February 17 the first fifteen of a total series of thirty telecasts was completed. These programs originated in the Francis Delafield Hospital of the Presbyterian Medical Center and appeared on a closed-circuit telecast in six cities beside Boston — namely, New York, Philadelphia, Pittsburgh, Toledo and Detroit and Dearborn, Michigan. These telecasts have been planned to sharpen the perceptions of all physicians in the early diagnosis and treatment of cancer, and the general opinion has been that the professional content of the telecasts has been of high quality.

It is of interest that in the record of attendance in the first eleven of these color telecasts — namely, through January 20 — Boston ranked second among the seven cities in which they appeared. It is also interesting that a substantial proportion of viewers, about 20 per cent, came from areas 15 or more miles and many of them more than 40 miles from Boston. A substantial number of the physicians in attendance, at least 25 per cent, were general practitioners.

The last fifteen telecasts, which are originating in the Memorial Hospital for Cancer in New York City, may be seen each Wednesday at 5 o'clock through June 2, in the Jimmy Fund Auditorium. Detailed programs have been mailed to all physicians in the Commonwealth.

KIDNEY SECTION

The Executive Committee of the Massachusetts Heart Association, as announced in a letter published elsewhere in this issue of the *Journal*, has approved a separation that at the same time represents a union. This consists of the formation in relation to

the Association of a kidney section; and a section, on the insistence of no less an authority than Noah Webster, is an "act or instance of cutting; separation by cutting; also a part separated; a division; portion; slice."

That this schism denotes also a union is adduced from the declaration by the president of the Association that for the first time in the United States "physicians representing two of the leading chronic diseases have joined together for scientific and public health purposes."

Those physicians of a generation now dwindling who were raised on the concept of a cardiorenal complex will rejoice both that the kidney is again coming into its own, even if under a cardiac aegis, and that by this action an increase in the number of fund drives for specific diseases has been for the moment averted.

The editors congratulate the Association on its new section and the cardiologists who comprise it on having added to their ranks more associates of a similar kidney.

The aggregate ages of 730 men who died in this city the past year amounted to 31,183 years, or an average of 42.7100 years each.
Boston M. & S. J., *March 8, 1854*

BOSTON MEDICAL LIBRARY

HENDRICK VAN DEVENTER

Hendrick van Deventer (1651–1724) is well known as a Dutch obstetrician who lived during the seventeenth and eighteenth centuries. The biography by Lamers (Lamers, A. J. M. Hendrick van Deventer, medicine doctor, 1651–1724. Leven en werken. Assen, 1946), recently acquired by the Library, discusses his life and character, as well as his interest in obstetrics, surgery, orthopedics and in public health. There are detailed bibliographic descriptions of his important books on obstetrics and rickets in Dutch and the translations into Latin, German, French and English, with a number of reproductions of title pages. He also wrote two theological books in 1708 and 1710. The text concludes with a chronologic list of his writings from 1696 to 1790, and a list of 51 writings about him.

MASSACHUSETTS DEPARTMENT OF MENTAL HEALTH

FURTHER INFORMATION ON MENTAL HOSPITALS

Mental hospitals, and general hospitals, are special environments constructed and maintained to care for people whose homes cannot supply the health resources they need at the particular moment. For example, if appendectomy is necessary the patient goes to a hospital that has the special facilities and personnel necessary for surgery. Mental hospitals as special environments offering health resources not available elsewhere in the community must be planned and operated around this concept. The following circumstances are essential:

Facilities to segregate the patient from the general public that he may be relieved of the demands made by his family, his work, his friends and the irritations of his environment (in a few cases the hospital must have additional facilities for segregation to protect the public from the patient).

Facilities and personnel to provide emotional support, affection, guidance, security and opportunity for learning new ways of thinking and living.

Most state hospitals effectively segregate the patients from the community, but the steps necessary for rehabilitation and for the development of increased stability are often neglected. Half-planned and half-supported hospitals ensure a steady inflow of patients, but by failing to provide the type of therapeutic environment necessary, they ensure also a steady accumulation of patients. In some cases the environment of a large state hospital not only fails to be therapeutic but, by its very organization, tends to aggravate the illness for which the patient was admitted.

For example, a patient may find his family ties undependable or may fail to find emotional support or sense of achievement in his work or solace in religion, and to protect himself from further pain distorts reality to a form more acceptable to him. Psychiatrists call this a psychosis. As one step in treatment the patient must be convinced that the world is after all a pleasant place in spite of its shortcomings. Instead of this he is placed in a hospital that is too crowded for comfort or privacy and cared for by physicians and nurses who are overworked, in an environment that seems to be intentionally planned to be artificial and unreal. Personal effects are taken away, quarters that are too cramped and too crowded are assigned, and the time, place and type of smoking, bathing and recreation are selected; diet is prescribed.

In such surroundings a patient has two choices. He can show further regression and withdrawal of all interest from the world around him, thus making

life in such circumstances bearable, or if he still has the strength and the ability to reason he can "take a flight into health" and, by recovering, escape from this environment. One suspects that his former environment seems good by comparison, and this may explain some of the "spontaneous remissions."

The mental hospital to be therapeutic must be in the charge of a physician who has a broad understanding of human needs, and who has great imagination in the planning of new and substitute ways of supplying such needs. He must be a person with the sensitivity for taking as much artificiality from the hospital environment as possible. It is obvious that he must be free to choose subordinates of all sorts who fit into this pattern of treatment. The staff must be able to enter knowingly into positive emotional relations with the patient. Everything done to the patient — his feeding, clothing, working, recreation and visiting privileges — plays an important part in his therapy. Obviously, this must be under the direction of the physician in charge. The entire staff must be indoctrinated and oriented to see how their particular function fits into the over-all plan of treatment. This goal is achieved in some parts, but not all parts, of the hospitals in Massachusetts. Other areas seem to be less fortunate.

Researches in this field are underway at the Boston State Hospital, the Boston Psychopathic Hospital, the Boston Veterans Administration Hospital, the Bedford Veterans Administration Hospital, the Metropolitan State Hospital and institutions in other states. These projects study the organization of the hospital personnel, the personal relations among various members of the staff, the staff and the patients and the patients with one another; these relations are known to play a definite part in the patient's course in the hospital. New methods of manipulating these forces are being studied. There is a great need for more intensive experimentation with the hospital environment as a therapeutic tool. It is hoped that more effective use can be made of the large hospitals.

JACK R. EWALT, M.D.
Commissioner

CORRESPONDENCE

HEART ASSOCIATION ADDS SECTION

To the Editor: At a meeting of the Executive Committee of the Massachusetts Heart Association on January 18, 1954, the formation of a kidney section was approved. This section has been activated as part of the Association by a committee consisting of John P. Merrill, M.D., chairman; Harry A. Derow, M.D.; Alexander Leaf, M.D.; Jack Metcoff, M.D.; Duncan Reid, M.D.; Arnold Relman, M.D.; and William B. Schwartz, M.D. Its purpose is to give formal acknowledgement of the important inter-relation between renal and heart disease, and between physiologic and clinical research in the two fields.

Furthermore, the formation of such a section recognizes the fact that the American Heart Association and its affiliate, the Massachusetts Heart Association, have substantially supported research in renal physiology and disease for some time. The relation between renal mechanisms and such entities as hypertensive disease and congestive heart failure is a natural precursor to the formation of such a group.

The purpose of the Kidney Section of the Massachusetts Heart Association is

To promote and encourage acquisition of new knowledge concerning renal disease and renal function, particularly as they affect cardiovascular disease.

To take all possible measures to inform the medical profession of advances in knowledge.

To keep the general public informed of progress with the end in view that hope and confidence will be inspired.

And to encourage the public support of the total program of the Massachusetts Heart Association to the end that a new and necessarily competitive and duplicating fund-raising effort for kidney disease should be made unnecessary.

At a meeting of the Executive Committee of the Kidney Section on January 21, 1954, Dr. Robert W. Wilkins, chairman of an American Heart Association committee to study the possibility of a kidney section within the national organization, discussed the problems and the possibilities on the national level. Dr. William Schwartz was named chairman of the first scientific meeting of the State section, which will be called in April, 1954. Its purpose will be to discuss in symposium form current concepts of the etiology, pathophysiology and treatment of renal diseases.

JOHN P. MERRILL, M.D.
Boston

HOLYOKE SOLDIERS' HOME

To the Editor: We wish to call to the attention of physicians in Massachusetts the fact that the Holyoke Soldiers' Home and Hospital is now in its second year of operation and that steady progress is being made in adopting the topmost policies and standards. The medical staff of this hospital is now holding regular monthly meetings. The following is a list of officers elected to the various committees:

MEDICAL STAFF OFFICERS

President, Edmund J. Zielinski, M.D., Holyoke; Vice-President, Alfred M. Glickman, M.D., Springfield; and Secretary-Treasurer, Thomas F. Ferriter, M.D., Springfield.

EXECUTIVE COMMITTEE

Edmund J. Zielinski, M.D., Holyoke
Alfred M. Glickman, M.D., Springfield
Thomas F. Ferriter, M.D., Springfield
Eugene W. Beauchamp, M.D., Springfield
Harry H. Michelson, M.D., Holyoke
Edwin Mahoney, M.D., Holyoke
John J. David, M.D., Springfield

MEDICAL RECORDS COMMITTEE

Samuel Potsubay, M.D., Holyoke, *Chairman*
Joseph R. Hobbs, M.D., Northampton
John A. Prybylo, M.D., Springfield

TISSUE COMMITTEE

H. Paul Wakefield, M.D., Holyoke
Samuel Klibanoff, M.D., Springfield
Robert Emery, M.D., Springfield

Further information may be obtained from the undersigned.

DAVID W. JOHNSON, M.D.
Medical Director
Soldiers' Home
Holyoke, Massachusetts

BULLETIN OF CANCER PROGRESS

To the Editor: Approximately 2500 physicians registered to practice medicine in Massachusetts are now receiving copies of *CA — A Bulletin of Cancer Progress* with the compliments of the Massachusetts Division of the American Cancer Society.

This bulletin is issued bimonthly by the parent organization, and we shall, on written request, be glad to mail a complimentary copy to any physician licensed to practice in Massachusetts.

GEORGE R. DUNLOP, M.D., *President*
American Cancer Society
(Massachusetts Division), Incorporated
Boston

ALCOHOLIC SYNONYMOUS

To the Editor: In the editorial, "Alcoholic Beverages," in the January 7 issue of the *Journal*, I found the comparisons of expenditures and costs of the various items in the national life most interesting.

It is not clear, however, whether the stated increase of 162 per cent in the consumption of beverage alcohol from 1934 to 1952 is based on dollar values or on gallons consumed. The merest statement of the economic facts is somewhat staggering. It would be an interesting experiment to determine whether a reduction in taxes assessed on alcohol and other products might be accompanied by a decrease in frustration and accompanying decrease in consumption of the taxed products. Frustration resulting from high taxes and governmental waste of natural resources is undoubtedly one of the factors responsible for the increase in the consumption of alcohol.

HARRY E. HANDLEY, M.D.
New York City

BOOK REVIEWS

Diseases of Muscle: A study in pathology. By Raymond D. Adams, M.A., M.D., D. Denny-Brown, M.D., D.Phil., F.R.C.P., and Carl M. Pearson, M.D., 8°, cloth, 556 pp., with 347 illustrations. New York: Paul B. Hoeber, Incorporated, 1953. $16.00.

This book fills a great void in the knowledge of muscular diseases. Throughout the past century clinicians have catalogued symptoms of muscular dysfunction into isolated patterns of disease. Continuing this trend, textbooks of medicine have attempted to group and classify a number of these recognized diseases but never in a logical fashion. This is the first serious attempt to resolve this enigma of nomenclature on the basis of known etiology and pathology.

Anatomy and physiology of muscles are reviewed. A critical survey of experimental studies of the pathologic reactions of muscles is given. The classification of muscular disease presented is incomplete, but it is based on etiology, when known, and otherwise on morbid anatomy. A great number of data have been collected by the authors. The book is profusely illustrated with excellent photomicrographs of the various pathological lesions. The recent and the pertinent older medical literature is covered in the bibliography. Although this book deals chiefly with the pathology of muscular diseases it contains much that should be most helpful to the clinician as well.

JOHN G. KUHNS, M.D.

Fundamentals of Clinical Orthopedics. By Peter A. Cassagrande, M.D., and Harold M. Frost, Jr., M.D. With forewords by Joseph S. Barr, M.D., and Frank N. Potts, M.D. 4°, cloth, 582 pp., with 390 illustrations. New York: Grune and Stratton, 1953. $18.50.

The ambitious title of this book is scarcely realized in the subject matter. It would be difficult to define or delimit the fundamentals of orthopedic surgery, but it certainly is not found in the descriptions of unusual diseases and the omission of the general rules of therapy in the more common orthopedic disturbances. The authors believe that a knowledge of so-called basic sciences is essential to orthopedic surgery, and metabolism, anatomy and microbiology are briefly described. There is much that is commendable in the volume. It is written in a lucid, readable style. The pictures are clear and well chosen for the most part. The chapters on trauma are good but scarcely adequate without recourse to other medical literature. The book is loosely arranged, with too much emphasis on the uncommon for general use by medical students. A bibliography of the recent pertinent medical literature would have been of value.

JOHN G. KUHNS, M.D.

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Surgery of the Pancreas. By Richard B. Cattell, M.D., surgeon, Lahey Clinic, New England Baptist Hospital and New England Deaconess Hospital; and Kenneth W. Warren, M.D., surgeon, Lahey Clinic, New England Baptist Hospital and New England Deaconess Hospital. 8°, cloth, 374 pp., with 100 illustrations and 41 tables. Philadelphia: W. B. Saunders Company, 1953. $10.00.

The authors have based this book on experience with over 1000 patients treated surgically at the Lahey Clinic. The chapters deal with anatomy and physiology, congenital malformations, acute and chronic relapsing pancreatitis, cysts, injuries, islet cells and hyperinsulinism, carcinoma and total pancreatectomy. Illustrative case histories are interspersed throughout the text. Bibliographies are appended to the chapters, and the literature is reviewed. There are indexes of authors and subjects. The illustrations and the publishing in general are excellent. The book is recommended for all medical libraries and to surgeons interested in the subject.

NOTICES

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on March 16 at noon. Dr. Sara M. Jordan will speak on the topic "Problems of Peptic Ulcer Reviewed."

PHI DELTA EPSILON FRATERNITY GRADUATE CLUB OF BOSTON

Alpha Theta Chapter, Phi Delta Epsilon, Tufts College Medical School, announces that the Aaron Brown Lecture will be given at the Beth Israel Hospital auditorium on March 22, at 8 p.m. Dr. C. P. Rhoads, director, Sloan–Kettering Institute for Cancer, will speak on the topic "Advances in Cancer Therapy." All interested persons are invited.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held at the Hotel Beaconsfield, Brookline, on Friday, April 9.

PROGRAM

8:00 a.m.–12:00 m. Operative schedules at different hospitals.

2:00 p.m.–3:00 p.m. Morbidity and Mortality Case Reports. Dr. Jacob Fine, Beverly, Massachusetts.

3:00 p.m.–4:00 p.m. Effects of Pentothal and Cyclopropane on Cardiac Output and Related Hemodynamics. Dr. Benjamin Etsten, Boston.

4:00 p.m.–5:00 p.m. Effects of Ether on Cardiac Output and Related Hemodynamics. Dr. William Brewster, Boston. (Moderator: Dr. Morris J. Nicholson, Boston.)

5:00 p.m.–7:00 p.m. Refreshments and dinner, Hotel Beaconsfield.

7:00 p.m.–7:30 p.m. Business meeting.

7:30 p.m.–9:00 p.m. The Clinical Use of the Muscle-Relaxing Agents in Anesthesia. Dr. Francis Foldes, Pittsburgh, Pennsylvania.

INTERNATIONAL POLIOMYELITIS CONGRESS

The third International Poliomyelitis Conference will be held at the University of Rome, Orthopedic Clinic, Rome, Italy, September 6 through 10.

INTERNATIONAL CONGRESS OF GYNECOLOGY AND OBSTETRICS

A meeting of the International Congress of Gynecology and Obstetrics will be held in Geneva July 26 through 31. The theme of the meeting will be "Prophylaxis in Gynecology and Obstetrics," and will be discussed by thirty-five speakers. Further information may be obtained from the Secretariat of the Congress, Maternité, Geneva, Switzerland.

INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE BRONCHI

The fourth congress of the International Association for the Study of the Bronchi will be held at Geneva on June 5 and 6. Professors Bruni (Milan), von Hayek (Vienna) and Latarjet (Lyon) will discuss the subject "The Vascularization of the Bronchi"; professors von Albertini (Zurich) and Galy (Lyon) will discuss "The Proper Classification of the Bronchial Adenomas of Jackson"; and Professor Brunner (Zurich) will present "The Indications and Results of Surgical Treatment of Bronchiectasis." Further information may be obtained from the president, Professor A. Montandon, director, Clinique universitaire d'O.R.L., Hôpital cantonal, Geneva, Switzerland.

STATE UNIVERSITY COLLEGE OF MEDICINE AT NEW YORK CITY

The annual Alumni Day of the State University College of Medicine at New York City will be celebrated on May 1. There will be a scientific session at Polhemus Clinical Hall and a business meeting in the morning, luncheon in the Nurses' Dining Room, Long Island College Hospital, and a dinner dance to benefit the research, scholarship and student-loan funds at the Hotel Granada, 268 Ashland Place, Brooklyn, at 7 p.m.

REVISTA BRASILEIRA DE GASTROENTEROLOGIA PRIZE

The *Revista Brasileira de Gastroenterologia*, in celebration of the first quinquennium of publication, will award a prize of $200 and a certificate of merit presented by the Brazilian Foreign Office for the best unpublished article on gastroenterology, proctology (medical or surgical) or allied subjects. The award will be made on July 15. Papers must be limited to 15 pages (22 x 29 centimeters), typewritten in any language on one side only and double spaced. They must be submitted to the Editor, *Revista Brasileira de Gastroenterologia*, Av. Graca Aranha, Rio de Janeiro, Brazil, accompanied by a summary and an entry letter, before May 1.

SOCIETY MEETINGS AND CONFERENCES

March 8. New England Cardiovascular Society. Page 304, issue of February 18.

March 8. Chelsea Soldiers' Home. Staff Meeting. Page 346, issue of February 25.

March 8–31. Consultation Clinics for Crippled Children. Page 305, issue of February 18.

March 9. Harvard Medical Society. Page 304, issue of February 18.

March 9, 16, April 8 and 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.

March 10. New England Pediatric Society. Page 346, issue of February 25.

March 10. Middlesex South District Medical Society. Page 346, issue of February 25.

March 11–13. American Orthopsychiatric Association. Page 129, issue of January 21.

March 12–May 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

March 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

March 15, April 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

March 16. South End Medical Club. Page 399.

March 20, April 17 and May 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.

March 22. Phi Delta Epsilon Fraternity Graduate Club of Boston. Page 399.

March 22–25. American Academy of General Practice. Page 129, issue of January 21.

March 24. Middlesex East District Medical Society.

March 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

March 28. National Gastroenterological Association. Page 265, issue of February 11.

March 31–April 2. American College of Surgeons. Sectional Meeting. Page 266, issue of February 11.

April 7. Massachusetts Academy of General Practice. Spring Clinical Assembly, New Bedford.

April 8–11. International Academy of Proctology. Page 130, issue of January 21.

April 9. New England Society of Anesthesiologists. Page 399.

April 10. American Congress of Physical Medicine. Page 266, issue of February 11.

April 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

April 21–24. Seminar and Conference on Cancer Cytology. Page 346, issue of February 25.

April 29, 30 and May 1. American Goiter Association. Somerset Hotel, Boston.

May 1. State University College of Medicine at New York City. Alumni Association. Notice above.

May 11. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)

May 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.

May 12. New England Obstetrical and Gynecological Society. Spring Meeting. Longmeadow Country Club, Springfield.

May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

May 31–June 3. American Urological Association. Page xvii, issue of July 23.

June 5 and 6. International Association for the Study of the Bronchi. Notice above.

June 17–19. American Geriatrics Society. Page 266, issue of February 11.

July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

July 23–29. International Cancer Congress. Page 914, issue of November 26.

July 26–31. International Congress of Gynecology and Obstetrics. Notice above.

September 6–10. International Poliomyelitis Congress. Page 399.

September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MARCH 11

THURSDAY, MARCH 11

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Lower Urinary-Tract Symptomatology and Treatment. Dr. Wyland F. Leadbetter. Regional Office of the Veterans Administration. Conference Room, 17 Court Street, Boston.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

8:30 p.m. Pentucket Association for Physicians. Present Trends in the Management of Breast Cancer. Dr. Joseph Tartakoff. Diburro Restaurant, Corner of Essex and Wingate streets, Haverhill.

FRIDAY, MARCH 12

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

(Notices concluded on page xxv)